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                 KAYKAVOOS"/AU OR "PARANG KEYKAVOUS"/AU)


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L2   ANSWER 1 OF 57  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:        2005:973071  HCAPLUS
TITLE:                   Recent advances in the discovery of Src kinase
                         inhibitors
AUTHOR(S):               Parang, Keykavous; Sun, Gongqin
CORPORATE SOURCE:        Department of Biomedical and Pharmaceutical Sciences,
                         University of Rhode Island, Kingston, RI, 02881, USA
SOURCE:                  Expert Opinion on Therapeutic Patents (2005), 15(9),
                         1183-1207
                         CODEN: EOTPEG; ISSN: 1354-3776
PUBLISHER:               Ashley Publications Ltd.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
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AB Src family kinases are involved in the regulation of a wide variety of normal cellular signal transduction pathways, such as cell growth, differentiation, survival, adhesion and migration. Considerable evidence implicates elevated expression and/or activity of Src kinases in many human cancers, osteoporosis, cardiovascular disorders and immune system dysfunction; thus, this family of protein tyrosine kinases now exists as intriguing targets for both basic research and drug discovery. Herein, a number of examples of currently developed Src family kinase inhibitors in selected patents from 2002 - 2005 will be described. Special attention will be made to the chemical diversity of ATP binding site inhibitors, potency, selectivity and therapeutic application of the compds.

L2 ANSWER 2 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:740638 HCAPLUS
TITLE: Regioselective solid-phase diphosphorylation and diphosphodithioation of unprotected nucleosides and carbohydrates
AUTHOR(S): Ahmadibeni, Yousef; **Parang, Keykavous**
CORPORATE SOURCE: Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005 (2005), ORGN-589. American Chemical Society: Washington, D. C.
CODEN: 69HFCL
DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)
LANGUAGE: English
AB Carbohydrate diphosphates are required for the biosynthesis of complex carbohydrates, glycoproteins, and glycolipids. Nucleosides diphosphates are intracellularly converted to nucleosides triphosphates in the presence of kinases. Organic chemists investigating these fields are required to prepare many kinds of pure nucleosides and carbohydrates monodiphosphates and monodiphosphodithioates in sufficient quantities. Two classes of aminomethyl polystyrene resin-bound linkers of p-acetoxybenzyl alc. were subjected to reactions with bis(2-cyanoethyl diisoproylphosphoramidite) to produce the corresponding polymer-bound phosphitylating reagents. Several unprotected nucleosides (e.g., thymidine, adenosine, AZT) and carbohydrates (e.g., galactose, mannose, melibiose) were reacted with the polymer-bound reagents. Oxidation with tert-Bu hydroperoxide or sulfurization with Beaucage's reagent, followed by removal of cyanoethoxy group with DBU, afforded the corresponding polymer-bound diphosphodiesters or diphosphodithioesters. The cleavage of polymer-bound compds. under acidic conditions afforded nucleosides and carbohydrates diphosphates and diphosphodithioates with high regioselectivity in 47-78% overall yield, while the linkers remained trapped on the resins.

L2 ANSWER 3 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:740637 HCAPLUS
TITLE: Regioselective solid-phase synthesis of dinucleoside and nucleoside-carbohydrate phosphodiesters and thiophosphodiesters using polymer-bound oxathiaphospholanes
AUTHOR(S): Ahmadibeni, Yousef; **Parang, Keykavous**
CORPORATE SOURCE: Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005 (2005), ORGN-588. American Chemical Society: Washington, D. C.
CODEN: 69HFCL
DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)
LANGUAGE: English
AB Nucleosides and carbohydrates phosphodiesters are of considerable interest in nucleic acid research and the development of nucleosides with improved antiviral activity and prodrugs containing masked phosphates. Dinucleoside phosphodiesters appear to be more stable than nucleoside monophosphates to non-specific phosphohydrolases. Two classes of polymer-bound N,N-diisopropylamino-1,3,2-oxathiaphospholane were synthesized and were reacted with unprotected carbohydrates (e.g., mannose, melibiose) and nucleosides (e.g., adenosine, uridine, thymidine, AZT) in the presence of 1H-tetrazole. Oxidation with tert-Bu hydroperoxide or sulfurization with Beaucage's reagent, followed by the 1,3,2-oxathiaphospholane ring-opening

with the same or different nucleosides or carbohydrates in the presence of DBU, afforded the corresponding sym. or unsym. dinucleoside and nucleoside-carbohydrate phosphodiesters and thiophosphodiesters derivs. through the elimination of polymer-bound ethylene episulfide in 36-70% overall yield. In total, by using different combinations of nucleosides and carbohydrates, 24 compds. (20 novel compds.) were synthesized. This strategy can be used to create the phosphodiester library of nucleosides and carbohydrates.

L2 ANSWER 4 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:740636 HCAPLUS
TITLE: Regioselective solid-phase synthesis of nucleosides and carbohydrates triphosphates and triphosphotrithioates
AUTHOR(S): Ahmadibeni, Yousef; **Parang, Keykavous**
CORPORATE SOURCE: Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005 (2005), ORGN-587. American Chemical Society: Washington, D. C.
CODEN: 69HFCL
DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)
LANGUAGE: English
AB Nucleosides are activated to triphosphate forms in the presence of kinases. Nucleosides triphosphates are required for the synthesis of nucleotides and nucleic acids and the biol. activity of nucleosides including several antiviral drugs. The regioselective synthesis of unprotected nucleosides and carbohydrate triphosphates is a challenging effort for organic chemists. Two classes of aminomethyl polystyrene resin-bound linkers of p-acetoxybenzyl alc. were subjected to reactions with a triphosphitylating reagent containing bis(1,3-diisoproylphosphoramidite) in the presence of 1H-tetrazole to yield the corresponding polymer-bound triphosphitylating reagents. A number of unprotected carbohydrates (e.g., galactose, mannose, melibiose) and nucleosides (e.g., thymidine, uridine, adenosine, AZT) were reacted with the polymer-bound reagents. Oxidation with tert-Bu hydroperoxide or sulfurization with Beaucage's reagent, followed by removal of cyanoethoxy group with DBU, afforded the polymer-bound triphosphodiesters or triphosphotrithiodiesters. The acidic cleavage of polymer-bound compds. with TFA gave nucleosides and carbohydrates triphosphates and triphosphotrithioates with high regioselectivity in 39-74 % overall yield.

L2 ANSWER 5 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:739913 HCAPLUS
TITLE: Converting a weak peptide inhibitor of Src kinase to potent peptide inhibitors by systemic structural modification
AUTHOR(S): Kumar, Anil; Wang, Yuehao; Sun, Gongqin; **Parang, Keykavous**
CORPORATE SOURCE: Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005 (2005), MEDI-405. American Chemical Society: Washington, D. C.
CODEN: 69HFCL
DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)
LANGUAGE: English
AB The design, synthesis, and evaluation of new compds. against Src tyrosine

kinases are attractive due to the association of Src tyrosine kinases activity with several diseases including cancer and osteoporosis. In contrast to ATP binding site, a few peptides have been identified as substrates for Src tyrosine kinases. Most of these peptide substrates are rather weak inhibitors with Km in high micromolar or in millimolar range. The best examples from these studies are peptides, Ac-YIYGSFK and Ac-CIYKYY, which were reported to be inhibitors of Src. Our radioactive kinase assay showed that Ac-YIYGSFK (IC50 = 570 μM) and Ac-CIYKYY (IC50 = 400 μM) were weak inhibitors of polyE4Y phosphorylation by active c-Src. We investigated whether by functional group modifications in the side chains of amino acids in Ac-CIYKYY, the inhibitory activity can be improved. The purpose of this study was to understand the structure-activity relationship of these compds. in order to develop novel Src inhibitors. Peptide Ac-CIYKF(NO2)Y, in which the nitrophenylalanine is located at position 5, exhibited a significantly higher inhibitory potency (IC50 = 0.53 μM) by approx. 750-fold vs. Ac-CIYKYY. Addnl., compds. with substituted halogens exhibited significantly high inhibitory potencies in the order of I > Cl > F. For example, Ac-CIYKF(4-I)Y exhibited (IC50 = 0.78 μM) approx. 510-fold higher inhibitory potency than Ac-CIYKYY. Mol. modeling studies showed that the intramol. hydrogen bonding of the amino group of the K4 with hydroxyl group of Y5 in Ac-CIYKYY is eliminated when the hydroxyl group is substituted with nitro group or halogens. It appears that the free amino group of the lysine is required for the interaction with the kinase domain of Src and generating inhibition. These results suggest that it is possible to convert a weak peptide inhibitor of Sc kinase to potent peptide inhibitors by systemic structural modifications.

L2 ANSWER 6 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:739912 HCAPLUS
TITLE: N-Heteroaromatic-peptide conjugates as Src kinase inhibitors
AUTHOR(S): Kumar, Anil; Wang, Yuehao; Sun, Gonquin; **Parang, Keykavous**
CORPORATE SOURCE: Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005 (2005), MEDI-404. American Chemical Society: Washington, D. C.
CODEN: 69HFCL
DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)
LANGUAGE: English

AB Src kinase exists as intriguing therapeutic target for drug discovery with respect to cancer and osteoporosis. Although selective inhibitors competitive with ATP have been synthesized for specific protein kinases, the process of inhibitor development is labor intensive due mainly to the presence of a large number of protein kinases that show a conserved ATP binding site. The main objective of this study was to exploit the ATP-binding site mol. recognition motif in combination with other recognition motifs. 3-Phenylpyrazolopyrimidine derivative, substituted with an alkyl carboxylic acid at N1 endocyclic amine, exhibited weak inhibitory potency (IC50 = 250 μM). Addnl., the radioactive kinase assay using polyE4Y as the substrate suggested that peptides YIYGSFK (IC50 = 570 μM) and Ac-CIYKYY (IC50 = 400 μM) were weak inhibitors of polyE4Y phosphorylation by active c-Src. More than fifty N-heteroarom.-peptide conjugates were synthesized using 3-pyrazolopyrimidine derivative as an ATP mimic and CIYKYY and YIYGSFK as peptide substrates. The carboxylic acid of substituted 3-phenylpyrazolopyrimidines was attached to the side chain of different amino acids in the peptide template. Two N-terminal

substituted 3-phenylpyrazolopyrimidine-peptide conjugates, 3-phenylpyrazolopyrimidine-CIYKYY (IC50 = 0.38 μM) and 3-phenylpyrazolopyrimidine-YIYGSFK (IC50 = 2.7 μM), inhibited the polyE4Y phosphorylation by active Src significantly higher than parent compds., N-heteroaroms. and peptides. This study suggests a synergistic inhibition effect of the conjugation of the ATP mimic with the peptide by possibly creating favorable interactions between the conjugate and the kinase domain. Mol. modeling studies of 3-phenylpyrazolopyrimidine-CIYKYY conjugate with Src suggested that the pyrazolopyrimidine ring binds to the ATP binding site and the peptide occupies the exterior space of the N-lobe in the kinase domain creating some new bonding interactions. This study suggests that weak inhibitors of Sc kinase can be conjugated to generate potent lead inhibitors that may be used for further optimization.

L2 ANSWER 7 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:739911 HCAPLUS
TITLE: Conformationally constrained peptide analogs of CIYKYY as inhibitors of Src tyrosine kinase
AUTHOR(S): Ye, Guofeng; Kumar, Anil; Wang, Yuehao; Sun, Gongqin; **Parang, Keykavous**
CORPORATE SOURCE: Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005 (2005), MEDI-403. American Chemical Society: Washington, D. C.
CODEN: 69HFCL
DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)
LANGUAGE: English
AB Peptide Ac-CIYKYY was a weak inhibitor (IC50 = 400 μM) of polyE4Y phosphorylation by active Src as shown by the radioactive kinase assay. Peptide Ac-CIYKF(NO2)Y, in which the nitrophenylalanine is located at Y5 position, exhibited a significantly higher inhibitory potency (IC50 = 0.53 μM) by approx. 750-fold vs. Ac-CIYKYY. Conformationally constrained derivs. of these compds. were synthesized by solid-phase methods to determine whether the presence of the constrained ring has any effect in inhibitory potency. Due to the presence of three tyrosine residues and one lysine in the C1I2Y3K4Y5Y6, there were several opportunities for linking side chains of amino acids. Four types of conformational constraints were introduced by linking head to tail, C-terminal to side chain, N-terminal to side chain, and side chain to side chain of the amino acids. The structure-activity relationships of these analogs and the comparison of their inhibitory potency with parent linear peptides are discussed.

L2 ANSWER 8 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:739886 HCAPLUS
TITLE: Synthesis and evaluation of hydroxamate derivatives as metal-mediated inhibitors of Csk
AUTHOR(S): Gu, Xianfeng; Wang, Yuehao; Kumar, Anil; Sun, Gonquin; **Parang, Keykavous**
CORPORATE SOURCE: Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005 (2005), MEDI-378. American Chemical Society: Washington, D. C.
CODEN: 69HFCL
DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)
LANGUAGE: English
AB In order to explore the possibility of designing metal-mediated inhibitors

against protein tyrosine kinases, a class of tyrosine and phenylalanine hydroxamate derivs. were synthesized (25 compds.) and evaluated for their ability to inhibit C-terminal Src kinase (Csk), a model tyrosine kinase, in the presence of cobalt. Tyrosine hydroxamate (IC50 = 9.5 μM) and phenylalanine hydroxamate (IC50 = 15.5 μM) inhibited Csk only in the presence of CoCl2. The presence of bulky groups (e.g., Cl, Br, I) or pyrazolopyrimidine on the Ph ring enhanced the inhibitory potency (IC50 = 2.0-6.3 μM), possibly due to the presence of interactions between these groups and a hydrophobic pocket in the enzyme. The substitution of amino group of hydroxamate with akyl or aryl groups or removal of α-amino group significantly reduced the inhibitory potency. These data suggest that specific functional groups are required for metal-binding affinity and inhibitors with better inhibitory profile can be designed.

L2 ANSWER 9 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:739730 HCAPLUS
TITLE: Studying the interactions of toxic metals with protein tyrosine kinases
AUTHOR(S): Ahmadibeni, Yousef; **Parang, Keykavous**; White, Millie; Sun, Gongqin
CORPORATE SOURCE: Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005 (2005), MEDI-219. American Chemical Society: Washington, D. C.
CODEN: 69HFCL
DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)
LANGUAGE: English
AB A number of tyrosine kinases are activated in the presence of toxic metals. The structural effects of binding of metals, such as arsenite, cadmium, lead, cobalt, and nickel, to tyrosine kinases were examined by CD anal. From all peptide sequences in different domains of c-Src containing one cysteine residue, only CPESLHDLMC in the CT lobe exhibited significant conformational changes. Two cysteine residues with a preserved 10-amino acid insert are also present in the C-terminal of Fyn, C-abl, Lck, Csk, and EGFR. Synthesized peptides containing these two cysteine residues and the whole c-Src and Csk proteins exhibited significant conformational changes in the presence of the metals. 113Cd NMR and 33S NMR studies of the peptide CPESLHDLMC confirmed the binding between the free sulfhydryl groups of the cysteine residues and cadmium. These results suggest that the cysteine residues in the C-terminal of tyrosine kinases are part of a common metal-binding domain.

L2 ANSWER 10 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:622866 HCAPLUS
DOCUMENT NUMBER: 143:243964
TITLE: Bisubstrate analog probes for the insulin receptor protein tyrosine kinase: Molecular yardsticks for analyzing catalytic mechanism and inhibitor design
AUTHOR(S): Hines, Aliya C.; **Parang, Keykavous**; Kohanski, Ronald A.; Hubbard, Stevan R.; Cole, Philip A.
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Bioorganic Chemistry (2005), 33(4), 285-297
CODEN: BOCMBM; ISSN: 0045-2068
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Bisubstrate analogs have the potential to provide enhanced specificity for protein kinase inhibition and tools to understand catalytic mechanism. Previous efforts led to the design of a peptide-ATP conjugate bisubstrate analog utilizing aminophenylalanine in place of tyrosine and a thioacetyl linker to the γ-phosphate of ATP which was a potent inhibitor of the insulin receptor kinase (IRK). In this study, the authors have examined the contributions of various electrostatic and structural elements in the bisubstrate analog to IRK binding affinity. Three types of changes (seven specific analogs in all) were introduced: a Tyr isostere of the previous aminophenylalanine moiety, modifications of the spacer between the adenine and the peptide, and deletions and substitutions within the peptide moiety. These studies allowed a direct evaluation of the hydrogen bond strength between the anilino nitrogen of the bisubstrate analog and the enzyme catalytic base Asp and showed that it contributes 2.5 kcal/mol of binding energy, in good agreement with previous predictions. Modifications of the linker length resulted in weakened inhibitory affinity, consistent with the geometric requirements of an enzyme-catalyzed dissociative transition state. Alterations in the peptide motif generally led to diminished inhibitory potency, and only some of these effects could be rationalized based on prior kinetic and structural studies. Taken together, these results suggest that a combination of mechanism-based design and empirical synthetic manipulation will be necessary in producing optimized protein kinase bisubstrate analog inhibitors.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 11 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:578716 HCAPLUS

DOCUMENT NUMBER: 143:243948

TITLE: Functional Diversity of Csk, Chk, and Src SH2 Domains due to a Single Residue Variation

AUTHOR(S): Ayrapetov, Marina K.; Nam, Nguyen Hai; Ye, Guofeng; Kumar, Anil; **Parang, Keykavous**; Sun, Gongqin

CORPORATE SOURCE: Department of Cell and Molecular Biology, University of Rhode Island, Kingston, RI, 02881, USA

SOURCE: Journal of Biological Chemistry (2005), 280(27), 25780-25787
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The C-terminal Src kinase (Csk) family of protein tyrosine kinases contains two members: Csk and Csk homologous kinase (Chk). Both phosphorylate and inactivate Src family kinases. Recent reports suggest that the Src homol. (SH) 2 domains of Csk and Chk may bind to different phosphoproteins, which provides a basis for different cellular functions for Csk and Chk. To verify and characterize such a functional divergence, we compared the binding properties of the Csk, Chk, and Src SH2 domains and investigated the structural basis for the functional divergence. First, the study demonstrated striking functional differences between the Csk and Chk SH2 domains and revealed functional similarities between the Chk and Src SH2 domains. Second, structural anal. and mutagenic studies revealed that the functional differences among the three SH2 domains were largely controlled by one residue, Glu127 in Csk, Ile167 in Chk, and Lys200 in Src. Mutating these residues in the Csk or Chk SH2 domain to the Src counterpart resulted in dramatic gain of function similar to Src SH2 domain, whereas mutating Lys200 in Src SH2 domain to Glu (the Csk

counterpart) resulted in loss of Src SH2 function. Third, a single point mutation of E127K rendered Csk responsive to activation by a Src SH2 domain ligand. Finally, the optimal phosphopeptide sequence for the Chk SH2 domain was determined These results provide a compelling explanation for the functional differences between two homologous protein tyrosine kinases and reveal a new structure-function relationship for the SH2 domains.
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 12 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:555141 HCAPLUS
TITLE: Racemic and optically active 2-methoxy-4-oxatetradecanoic acids: novel synthetic fatty acids with selective antifungal properties
AUTHOR(S): Carballeira, Nestor M.; O'Neill, Rosann; **Parang, Keykavous**
CORPORATE SOURCE: Department of Chemistry, University of Puerto Rico, San Juan, 00931-3346, P. R.
SOURCE: Chemistry and Physics of Lipids (2005), 136(1), 47-54
CODEN: CPLIA4; ISSN: 0009-3084
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The unprecedented (±)-2-methoxy-4-oxatetradecanoic acid and the optically pure (S)-2-methoxy-4-oxatetradecanoic acid were synthesized in 6 steps and in 11-14% overall yields starting with either 1,2-O-isopropylidene-rac-glycerol or 1,2-O-isopropylidene-(S)-glycerol. The key step in the synthesis was the selective monosilylation of a dibutylstannylene intermediate. The title compds. displayed selective fungitoxicity in the range of 0.08-0.22 mM against Cryptococcus neoformans ATCC 66031 and Aspergillus niger ATCC 16404, but no significant activity against Candida albicans ATCC 14053 and ATCC 60193 (>2.6 mM). Albeit being good substrates for N-myristoyltransferases (NMTs), the racemic and the S-enantiomer of the oxygenated 2-methoxylated compds. showed no significant difference in antifungal activity. This finding suggests an alternative mechanism of fungitoxicity other than NMT inhibition.
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 13 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:310131 HCAPLUS
DOCUMENT NUMBER: 143:7928
TITLE: Polymer-Bound Oxathiaphospholane: A Solid-Phase Reagent for Regioselective Mono-Thiophosphorylation and Mono-Phosphorylation of Unprotected Nucleosides and Carbohydrates
AUTHOR(S): Ahmadibeni, Yousef; **Parang, Keykavous**
CORPORATE SOURCE: Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Organic Letters (2005), 7(10), 1955-1958
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two polymers bound to N,N-diisopropylamino-1,3,2-oxathiaphospholane were reacted with unprotected carbohydrates and nucleosides in the presence of 1H-tetrazole, followed by oxidation with tert-Bu hydroperoxide or sulfurization with Beaucage's reagent. The 1,3,2-oxathiaphospholane ring-opening with 3-hydroxy-propionitrile, followed by treatment with DBU,

afforded the corresponding monophosphate and mono-thiophosphate derivs., resp., through the elimination of polymer-bound ethylene epi-sulfide. Reactions using this strategy offer the advantages of high regioselectivity, mono-substitution, and facile isolation and recovery of products.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 14 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:76219 HCAPLUS
DOCUMENT NUMBER: 142:177041
TITLE: Preparation of azole monosaccharide as antifungal agents
INVENTOR(S): **Parang, Keykavous**; Sardari, Soroush; Nam, Nguyen Hai
PATENT ASSIGNEE(S): The Board of Governors for Higher Education State of Rhode Island and Providence Plantations, USA
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005006860	A2	20050127	WO 2004-US23316	20040719
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.: US 2003-488319P P 20030718
US 2004-543972P P 20040212

OTHER SOURCE(S): MARPAT 142:177041
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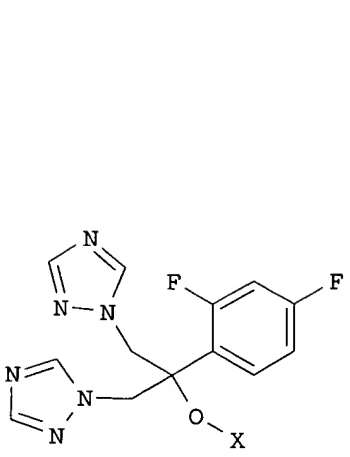

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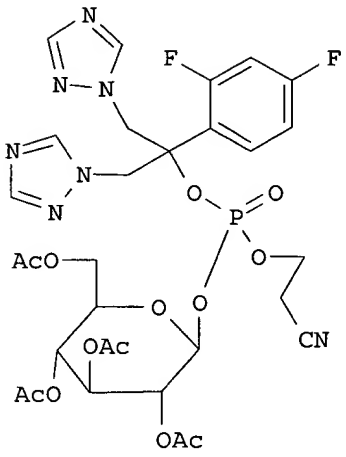


II

AB The present invention is broadly directed to azole derivs. I, wherein X is COR, P(O)(OR1)(OR2); R is alkyl, aryl, alkene, alkyne, alkyl halide, alkoxy, aryloxy; R1 is H, alkyl, aryl; R2 is alkyl, aryl, alkene, alkyne, alkyl halide, ester substituted six or five member cyclic monosaccharide, that exhibit antifungal activity and methods for making the same. In one aspect, the invention includes carboxylic acid and phosphate ester derivs. of fluconazole that exhibit antifungal activity. In addition, the invention comprises methods for synthesizing the derivs. and pharmaceutical compns. containing the derivs. Thus, monosaccharide II was prepared and tested in vitro as antifungal agent.

L2 ANSWER 15 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:31514 HCAPLUS
DOCUMENT NUMBER: 142:298278
TITLE: Solid-Phase Reagents for Selective Mono-Phosphorylation of Carbohydrates and Nucleosides
AUTHOR(S): Ahmadibeni, Yousef; **Parang, Keykavous**
CORPORATE SOURCE: Department of Biomedical and Pharmaceutical Sciences College of Pharmacy, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Journal of Organic Chemistry (2005), 70(3), 1100-1103 CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two classes of aminomethyl polystyrene resin-bound linkers of p-acetoxybenzyl alc. were subjected to reactions with 2-cyanoethyl N,N-diisopropylchlorophosphoramidite to produce the corresponding polymer-bound phosphitylating reagents. These were reacted with a number of unprotected nucleosides and carbohydrates in the presence of 1H-tetrazole. Oxidation with tert-Bu hydroperoxide followed by removal of the cyanoethoxy group with 1,8-diazabicyclo[5.4.0]undec-7-ene afforded the corresponding polymer-bound phosphate diesters. Acidic cleavage of the p-acetoxybenzyl alc. linker yielded mono-phosphorylated products with high regioselectivity and trapped linkers on the resins that can be reused.
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 16 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:31216 HCAPLUS
DOCUMENT NUMBER: 142:275949
TITLE: Probing the Communication between the Regulatory and Catalytic Domains of a Protein Tyrosine Kinase, Csk
AUTHOR(S): Lin, Xiaofeng; Ayrapetov, Marina K.; Lee, Sungsoo; **Parang, Keykavous**; Sun, Gongqin
CORPORATE SOURCE: Department of Cell and Molecular Biology and Department of Biomedical Sciences, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Biochemistry (2005), 44(5), 1561-1567
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Protein tyrosine kinases (PTKs) are important regulators of mammalian cell function, and their own activities are tightly regulated. Underlying their tight regulation, all PTKs contain multiple regulatory domains in addition to a catalytic domain. C-terminal Src kinase (Csk) contains a catalytic domain and a regulatory region, consisting of an SH3 and an SH2 domain. In this study, we probed the communication between the regulatory and catalytic domains of Csk. First, kinetic characterization of SH3 and SH2 domain deletion mutants demonstrated that the SH3 and SH2 domains were crucial in maintaining the full activity of Csk, but were not directly involved in Csk recognition of its physiol. substrate, Src. Second, highly conserved Trp188, corresponding to a key residue in domain-domain communication in other PTKs, was found to be important for maintaining the active structure of Csk by the presence of the regulatory region, but not required for Csk activation triggered by a phosphopeptide binding to the SH2 domain. Third, structural alignment indicated that the presence of the regulatory domains modulated the conformation of multiple substructures in the catalytic domain, some directly and others remotely. Mutagenic and kinetic studies supported this assignment. This report extended previous studies of Csk domain-domain communication, and provided a foundation for further detailed investigation of this communication.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 17 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:916843 HCAPLUS
DOCUMENT NUMBER: 142:32454
TITLE: Carboxylic acid and phosphate ester derivatives of fluconazole: synthesis and antifungal activities
AUTHOR(S): Nam, Nguyen-Hai; Sardari, Soroush; Selecky, Meredith; **Parang, Keykavous**
CORPORATE SOURCE: Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Bioorganic & Medicinal Chemistry (2004), 12(23), 6255-6269
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 142:32454

AB Two classes of fluconazole derivs., (a) carboxylic acid esters and (b) fatty alc. and carbohydrate phosphate esters, were synthesized and evaluated in vitro against Cryptococcus neoformans, Candida albicans, and Aspergillus niger. All carboxylic acid ester derivs. of fluconazole, such as O-2-bromooctanoylfluconazole (MIC = 111 μg/mL) and O-11-bromoundecanoylfluconazole (MIC = 198 μg/mL), exhibited higher

antifungal activity than fluconazole (MIC ≥ 4444 μg/mL) against C. albicans ATCC 14053 in SDB medium. Several fatty alc. phosphate triester derivs. of fluconazole exhibited enhanced antifungal activities against C. albicans and/or A. niger compared to fluconazole in SDB medium. For example, 2-cyanoethyl-ω-undecylenyl fluconazole phosphate with MIC value of 122 μg/mL had at least 36 times greater antifungal activity than fluconazole against C. albicans in SDB medium. Methyl-undecanyl fluconazole phosphate with a MIC value of 190 μg/mL was at least 3-fold more potent than fluconazole against A. niger ATCC 16404. All compds. had higher estimated lipophilicity and dermal permeability than those for fluconazole. These results demonstrate the potential of these antifungal agents for further development as sustained-release topical antifungal chemotherapeutic agents.

REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 18 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:891773 HCAPLUS
DOCUMENT NUMBER: 142:70676
TITLE: ATP-phosphopeptide conjugates as inhibitors of Src tyrosine kinases
AUTHOR(S): Nam, Nguyen-Hai; Lee, Sungsoo; Ye, Guofeng; Sun, Gongqin; **Parang, Keykavous**
CORPORATE SOURCE: Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy, The University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Bioorganic & Medicinal Chemistry (2004), 12(22), 5753-5766
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 142:70676
AB A number of Src SH2 domain inhibitors enhance the kinase catalytic activity by switching the closed inactive to the open active conformation. ATP-phosphopeptide conjugates were designed and synthesized as Src tyrosine kinase inhibitors based on a tetrapeptide sequence pTyr-Glu-Glu-Ile (pYEEI) and ATP to block the SH2 domain signaling and substrate phosphorylation by ATP, resp. In general, ATP-phosphopeptide conjugates with optimal linkers such as compds. 5 and 7 (Ki = 1.7-2.6 μM) showed higher binding affinities to the ATP-binding site relative to the other ATP-phosphopeptide conjugates having short or long linkers, 1-4 and 6, (Ki = 10.1-16.1 μM) and ATP (Km = 74 μM). These ATP-phosphopeptide conjugates may serve as novel templates for designing protein tyrosine kinase inhibitors to block SH2 mediated protein-protein interactions and to counter the activation of enzyme that resulted from the SH2 inhibition.
REFERENCE COUNT: 79 THERE ARE 79 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 19 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:839015 HCAPLUS
DOCUMENT NUMBER: 142:168609
TITLE: Design strategies for protein kinase inhibitors
AUTHOR(S): **Parang, Keykavous**; Sun, Gongqin
CORPORATE SOURCE: Department of Biomedical and Pharmaceutical Sciences, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Current Opinion in Drug Discovery & Development (2004), 7(5), 617-629
CODEN: CODDFF; ISSN: 1367-6733

PUBLISHER: Thomson Scientific
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The deregulation of protein kinases due to mutation or overexpression is a hallmark of several diseases, e.g., cancer, diabetes, inflammation, and cardiovascular disorders. Consequently, there has been a growing interest in the discovery of protein kinase inhibitors as novel drugs. Here, the authors focus on key milestones and advances in protein kinase inhibitor drug discovery over the last year, with an emphasis on novel strategies such as targeting of single and multiple binding sites, inactive conformations of kinases allosteric sites, regulatory domains, and heat shock proteins. The authors highlight recent developments for specific inhibitors in clin. studies for growth factor receptors, non-receptor tyrosine kinases and serine/threonine kinases.
REFERENCE COUNT: 139 THERE ARE 139 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 20 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:581031 HCAPLUS
DOCUMENT NUMBER: 141:309958
TITLE: Copper dipicolinates as peptidomimetic ligands for the Src SH2 domain
AUTHOR(S): Schmidt, Boris; Jiricek, Jan; Titz, Alexander; Ye, Guofeng; **Parang, Keykavous**
CORPORATE SOURCE: Institute for Organic Chemistry and Biochemistry, Darmstadt Technical University, Darmstadt, D-64287, Germany
SOURCE: Bioorganic & Medicinal Chemistry Letters (2004), 14(16), 4203-4206
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:309958
AB The introduction of copper chelates into peptide mimetics creates the Src SH2 binding ligands and paramagnetic complexes suitable for EPR studies of peptide protein interactions. The dipicolinic acid was attached to SH2 domain targeting fragments by two different linkers.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 21 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:377215 HCAPLUS
DOCUMENT NUMBER: 141:89359
TITLE: Conformationally Constrained Peptide Analogues of pTyr-Glu-Glu-Ile as Inhibitors of the Src SH2 Domain Binding
AUTHOR(S): Nam, Nguyen-Hai; Ye, Guofeng; Sun, Gongqin; **Parang, Keykavous**
CORPORATE SOURCE: Department of Biomedical Sciences and Department of Cell and Molecular Biology, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Journal of Medicinal Chemistry (2004), 47(12), 3131-3141
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of conformationally-constrained peptides were designed and

synthesized as the Src SH2 domain ligands based on a tetrapeptide sequence pTyr-Glu-Glu-Ile (pYEEI). In general, the constrained peptides showed higher binding affinities to the Src SH2 domain relative to the corresponding linear peptides as evaluated by a fluorescence polarization assay. Mol. modeling studies revealed that in constrained peptides, the isoleucine side chain penetrates very deeply into the hydrophobic binding pocket (P + 3 site) of the Src SH2 domain. These constrained peptides can serve as novel templates for the design of small and nonpeptidic inhibitors of the Src SH2 domain.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 22 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:298961 HCAPLUS
DOCUMENT NUMBER: 141:277230
TITLE: Total synthesis and in vitro antifungal activity of (±)-2-methoxytetradecanoic acid
AUTHOR(S): Carballeira, Nestor M.; Ortiz, Denisse; **Parang, Keykavous**; Sardari, Soroush
CORPORATE SOURCE: Department of Chemistry, University of Puerto Rico, San Juan, 00931-3346, P. R.
SOURCE: Archiv der Pharmazie (Weinheim, Germany) (2004), 337(3), 152-155
CODEN: ARPMAS; ISSN: 0365-6233
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:277230

AB The marine fatty acid (±)-2-methoxytetradecanoic acid was synthesized in two steps (71% overall yield) starting from com. available Me 2-hydroxytetradecanoate. The total synthesis of title racemic was accomplished by methylating com. available Me 2-hydroxytetradecanoate with Me iodide and hydrolysis with sodium hydride in DMSO which afforded Me 2-methoxytetradecanoic acid. The title compound was antifungal against Candida albicans (ATCC 14053) in RPMI medium and Aspergillus niger (ATCC 16404) and Cryptococcus neoformans (ATCC 66031) in SDB medium at the min. inhibitory concentration (MIC) of 100 mM, which compares to the fungi-toxicity of a 2-iodotetradecanoic acid against the same fungi. The title compound was also five to ten times more cytotoxic than capric acid to C. albicans and A. niger in the tested medium but comparable in cytotoxicity to either capric acid and its 2-methoxylated analog to C. neoformans. The antifungal activity of (±)-2-methoxytetradecanoic acid is explained in terms of inhibition of N-myristoyltransferase.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 23 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:192742 HCAPLUS
DOCUMENT NUMBER: 141:306676
TITLE: Inhibitors of Protein Kinase Signaling Pathways
AUTHOR(S): Force, Thomas; Kuida, Keisuke; Namchuk, Mark; **Parang, Keykavous**; Kyriakis, John M.
CORPORATE SOURCE: Molecular Cardiology Research Institute, Tufts-New England Medical Center and Tufts University School of Medicine, Boston, MA, USA
SOURCE: Circulation (2004), 109(10), 1196-1205
CODEN: CIRCAZ; ISSN: 0009-7322
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Protein kinases are enzymes that covalently modify proteins by attaching phosphate groups (from ATP) to serine, threonine, and/or tyrosine residues. In so doing, the functional properties of the protein kinase's substrates are modified. Protein kinases transduce signals from the cell membrane into the interior of the cell. Such signals include not only those arising from ligand-receptor interactions but also environmental perturbations such as when the membrane undergoes mech. deformation (ie, cell stretch or shear stress). Ultimately, the activation of signaling pathways that use protein kinases often culminates in the reprogramming of gene expression through the direct regulation of transcription factors or through the regulation of mRNA stability or protein translation. Protein kinases regulate most aspects of normal cellular function. The pathophysiol. dysfunction of protein kinase signaling pathways underlies the mol. basis of many cancers and of several manifestations of cardiovascular disease, such as hypertrophy and other types of left ventricular remodeling, ischemia/reperfusion injury, angiogenesis, and atherogenesis. Given their roles in such a wide variety of disease states, protein kinases are rapidly becoming extremely attractive targets for drug discovery, probably second only to heterotrimeric G protein-coupled receptors (eg, angiotensin II). Here, we will review the reasons for this explosion in interest in inhibitors of protein kinases and will describe the process of identifying novel drugs directed against kinases. We will specifically focus on disease states for which drug development has proceeded to the point of clin. or advanced preclin. studies.

REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 24 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:94576 HCAPLUS

DOCUMENT NUMBER: 140:350021

TITLE: Design of tetrapeptide ligands as inhibitors of the Src SH2 domain

AUTHOR(S): Nam, Nguyen-Hai; Pitts, Rebecca L.; Sun, Gongqin; Sardari, Soroush; Tiemo, Amie; Xie, Mingxing; Yan, Bingfang; **Parang, Keykavous**

CORPORATE SOURCE: College of Pharmacy, Department of Biomedical Sciences, The University of Rhode Island, Kingston, RI, 02881, USA

SOURCE: Bioorganic & Medicinal Chemistry (2004), 12(4), 779-787
CODEN: BMECEP; ISSN: 0968-0896

PUBLISHER: Elsevier Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Src homol.-2 (SH2) domains are noncatalytic motifs containing approx. 100 amino acid residues that are involved in intracellular signal transduction. The phosphotyrosine-containing tetrapeptide pTyr-Glu-Glu-Ile (pYEEI) binds to Src SH2 domain with high affinity (Kd = 100 nM). The development of five classes of tetrapeptides as inhibitors for the Src SH2 domain is described. Peptides were prepared via solid-phase peptide synthesis and tested for affinity to Src SH2 domain using a fluorescence polarization based assay. All of the N-terminal substituted pYEEI derivs. (class II) presented binding affinity (IC50 = of 2.7-8.6 μM) comparable to pYEEI (IC50 = 6.5 μM) in this assay. C-Terminal substituted pYEEI derivs. (class III) showed a lower binding affinity with IC50 values of 34-41 μM. Amino-substituted phenylalanine derivs. (class IV) showed weak binding affinities (IC50 = 16-153 μM). Other substitutions on Ph ring (class I) or the replacement of the Ph ring with other cyclic groups

(class V) dramatically decreased the binding of tetrapeptides to Src SH2 (IC50 > 100 μM). The ability of pYEEI and several of the tetrapeptides to inhibit the growth of cancer cells were assessed in a cell-based proliferation assay in human embryonic kidney (HEK) 293 tumor cells. The binding affinity of several of tested compds. against Src SH2 domain correlates with antiproliferative activity in 293T cells. None of the compds. showed any significant antifungal activity against Candida albicans ATCC 14053 at the maximum tested concentration of 10 μM. Overall, these results provided the structure-activity relationships for some FEEI and YEEI derivs. designed as Src SH2 domain inhibitors.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 25 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:992912 HCAPLUS
DOCUMENT NUMBER: 140:177191
TITLE: Determination of the substrate-docking site of protein tyrosine kinase C-terminal Src kinase
AUTHOR(S): Lee, Sungsoo; Lin, Xiaofeng; Nam, Nguyen Hai; **Parang, Keykavous**; Sun, Gongqin
CORPORATE SOURCE: Departments of Cell and Molecular Biology, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2003), 100(25), 14707-14712 CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Protein tyrosine kinases (PTK) are key enzymes of mammalian signal transduction. For the fidelity of signal transduction, each PTK phosphorylates only one or a few proteins on specific Tyr residues. Substrate specificity is thought to be mediated by PTK-substrate docking interactions and recognition of the phosphorylation site sequence by the kinase active site. However, a substrate-docking site has not been determined on any PTK. C-terminal Src kinase (Csk) is a PTK that specifically phosphorylates Src family kinases on a C-terminal Tyr. In this study, by sequence alignment and site-specific mutagenesis, we located a substrate-docking site on Csk. Mutations in the docking site disabled Csk to phosphorylate, regulate, and complex with Src but only moderately affected its general kinase activity. A peptide mimicking the docking site potently inhibited (IC50 = 21 μM) Csk phosphorylation of Src but only moderately inhibited (IC50 = 422 μM) its general kinase activity. Determination of the substrate-docking site provides the structural basis of substrate specificity in Csk and a model for understanding substrate specificity in other PTKs.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 26 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:924736 HCAPLUS
DOCUMENT NUMBER: 140:209724
TITLE: Protein kinases and their modulation in the central nervous system
AUTHOR(S): Sardari, S.; Pourmorad, F.; Tiemo, A.; Nam, N. H.; **Parang, K.**
CORPORATE SOURCE: Department of Biomedical Sciences, College of Pharmacy, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Current Medicinal Chemistry: Central Nervous System

Agents (2003), 3(4), 341-364
CODEN: CMCCCO; ISSN: 1568-0150
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Protein kinases (PKs) mediate neuronal morphol., differentiation, survival, repair, and plasticity in central nervous system (CNS). In this review, the structure and function of PKs involved in CNS function, various neurol. disorders, learning process, and memory are discussed. Certain types of PKs and their ligands have been implicated in memory and learning, axon guidance, the formation of neural projections, axon fasciculation, cell migration, and neurotrophin signaling. Many of these functions are regulated via the action of protein tyrosine kinases (PTKs) and their ligands, such as epidermal growth factor (EGF) receptor, Janus kinase-signal transducer and activator of transcription (JAK/STAT), Fyn-tyrosine kinase, Eph receptors, and neurotrophins (NTs) [e.g., brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF)]. Serine/threonine kinases, such as activins, bone morphogenic proteins (BMPs), mitogen-activated protein (MAP) kinases (e.g., p44/42 MAPK, c-Jun N-terminal kinase, p38 MAPKs), and protein kinases A (PKA) and C (PKC) and their function in the CNS are also discussed. The role of protein kinase inhibitors (PKIs), isolated from microbial, botanical sources or synthesized by conventional approaches, in determining CNS signaling cascades and function, and the treatment of neurol. disorders is reviewed.
REFERENCE COUNT: 407 THERE ARE 407 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 27 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:701491 HCAPLUS
DOCUMENT NUMBER: 140:23107
TITLE: Anti-HIV Design. [In: Curr. Pharm. Des., 2003; 9(22)]
AUTHOR(S): **Parang, K.**; Editor
CORPORATE SOURCE: United Arab Emirates
SOURCE: (2003) Publisher: (Bentham Science Publishers Ltd.: Sharjah, United Arab Emirates), 71 pp.
DOCUMENT TYPE: Book
LANGUAGE: English
AB Unavailable

L2 ANSWER 28 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:634960 HCAPLUS
TITLE: Modeling of activity for biological samples using artificial neural network
AUTHOR(S): Sardari, S.; **Parang, K.**
CORPORATE SOURCE: Department of Biomedical Sciences, University of Rhode Island, Kingston, RI, 02881-0809, USA
SOURCE: Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), MEDI-352. American Chemical Society: Washington, D. C.
CODEN: 69EKY9
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Purpose: The applicability of artificial neural network (ANN) modeling to bioactivity determination of a group of natural product samples based on bioinformatic descriptors, laboratory data and database indexing terms is studied. Method: The system of analyzing large amts. of indexing term from CA database, using ANN is presented. The architecture was optimized

to prevent memorization while maximizing the efficiency. The group of selected descriptors applied into the optimized ANN included designated taxonomic position of the sources, DNA-C values, chemical, ecol. and bioactivity notions. The predictability of the model was tested on members of the training and test groups. Results: The average error of 0.049 for a target of 0.05 after 63 cycles was obtained. The relative importance for descriptor data was pooled. The top three were biol. activity, DNA values and chemical notion. Predictability of the model was %95.00. The applicability of database terms in such modeling has been discussed.

L2 ANSWER 29 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:617637 HCAPLUS
DOCUMENT NUMBER: 139:276446
TITLE: Reactions of Solid-Supported Reagents and Solid Supports with Alcohols and Phenols through Their Hydroxyl Functional Group
AUTHOR(S): Nam, Nguyen-Hai; Sardari, Soroush; **Parang, Keykavous**
CORPORATE SOURCE: Department of Biomedical Sciences, College of Pharmacy, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Journal of Combinatorial Chemistry (2003), 5(5), 479-546
CODEN: JCCHFF; ISSN: 1520-4766
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review discusses the attachment of alcs. and phenols to resins through reactions with either supported reagents or with the supports themselves. The reactions of alcs. and phenols with solid-supported reagents, the attachment of alcs. and phenols as ethers and esters through Mitsunobu reactions, the synthesis and functionalization of carbohydrates on solid support, the synthesis of oligonucleotides on solid support, and miscellaneous other methods for the attachment of alcs. and phenols to supports are discussed in the review.
REFERENCE COUNT: 434 THERE ARE 434 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 30 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:89031 HCAPLUS
DOCUMENT NUMBER: 139:46173
TITLE: Current targets for anticancer drug discovery
AUTHOR(S): Nam, Nguyen-Hai; **Parang, Keykavous**
CORPORATE SOURCE: Department of Biomedical Sciences, College of Pharmacy, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Current Drug Targets (2003), 4(2), 159-179
CODEN: CDTUAU; ISSN: 1389-4501
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The call for the discovery of less toxic, more selective, and more effective agents to treat cancer has become more urgent. Inhibition of angiogenesis continues to be one of the main streams in the current cancer drug discovery activity. Insights into tumor angiogenesis biol. have led to the identification of a number of mols., which are important for the progression of these processes. Of particular interest is a group of growth factors including fibroblast growth factor, platelet-derived growth

factor, and vascular endothelial growth factor. These growth factors and their corresponding receptor tyrosine kinases have become important targets for inhibition of the proliferation of endothelial cells, the main component of blood vessels. The validated targets for inhibition of angiogenesis also include a family of matrix metalloproteinases and cell adhesion mols. In the closely related area, protein kinases have emerged as one of the most important targets for drug discovery. Besides growth factor receptor tyrosine kinases, numerous other protein kinases implicated in malignancies have been identified including non-receptor kinases such as Bcl-Abl and Src kinases. In addition, the cell cycle regulators (cyclin-dependent kinases, p21 gene) and apoptosis modulators (Bcl-2 oncoprotein, p53 tumor suppressor gene, survivin protein, etc) have also attracted renewed interest as potential targets for anticancer drug discovery. Other mol. targets include protein farnesyltransferase (FTase), histone deacetylase (HDAC), and telomerase, which have essential roles in cellular signal transduction pathways (FTase, HDAC) and cell life span (telomerase). This review presents a comprehensive summary and discussion on the most important targets currently attracting a great deal of interest in contemporary anticancer drug design and discovery. Recent advances complementing these targets are also highlighted.

REFERENCE COUNT: 147 THERE ARE 147 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 31 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:617960 HCAPLUS

TITLE: Design and synthesis of peptide analogues as inhibitors of Src tyrosine kinase

AUTHOR(S): Pitts, Rebecca L.; **Parang, Keykavous**; Sun, Gonquin

CORPORATE SOURCE: Biomedical Sciences, University of Rhode Island, Kingston, RI, 02881, USA

SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), MEDI-107. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ

DOCUMENT TYPE: Conference; Meeting Abstract

LANGUAGE: English

AB The role of Src tyrosine kinase in disease states including cancer has been well elucidated. The rational design and synthesis of potent Src inhibitors provides an attractive target in the development of anti-cancer agents. Src homol.-2 (SH2) domains are noncatalytic motifs that recognize phosphorylated tyrosine (pTyr) residues on substrate proteins and elicit phosphorylation events downstream in the signaling pathway. Affinity of the SH2 domain to phosphopeptide substrates is highly dependent on the amino acid sequence C-terminal to the pTyr. The affinity of the tetrapeptide pTyr-Glu-Glu-Ile (pYEEI) to Src SH2 domains presents a lead structure in the rational design of Src inhibitors. Several unnatural Y*EEI and F*EEI (* is a substituent(s); e.g. -I, -F, -NO2) tetrapeptides have been synthesized via solid phase peptide synthesis and assayed against Src SH2. Early work using 4-nitrophenylalanine in the pTyr position failed to yield a compound more potent than the endogenous ligand (Kd > 1000 nM). However, reduction of the nitro group allows subsequent substitution of anionic groups to mimic the interactions of pTyr with the SH2 domain. This current investigation focuses on the design and synthesis of a small library of such derivs. whose affinity to Src SH2 domain are evaluated by fluorescence polarization.

L2 ANSWER 32 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2002:481780 HCAPLUS
DOCUMENT NUMBER: 137:325588
TITLE: Polymer-supported reagents for methylphosphorylation and phosphorylation of carbohydrates
AUTHOR(S): **Parang, Keykavous**
CORPORATE SOURCE: Department of Biomedical Sciences, College of Pharmacy, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2002), 12(14), 1863-1866
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:325588
AB Two polymer-supported reagents for methylphosphorylation and phosphorylation of carbohydrates have been developed. P-Hydroxybenzyl alc. and β-mercaptoethanol were immobilized on cross-linked divinylbenzene-polystyrene copolymer and conjugated with Me N,N-diisopropylchlorophosphoramidite. Carbohydrates were reacted with polymer-bound phosphitylating reagents. Further oxidation, with or without the methoxy group deprotection, and cleavage yielded methylphosphorylated or phosphorylated carbohydrates, resp.
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 33 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:440277 HCAPLUS
DOCUMENT NUMBER: 138:100144
TITLE: Designing bisubstrate analog inhibitors for protein kinases
AUTHOR(S): **Parang, Keykavous**; Cole, Philip A.
CORPORATE SOURCE: College of Pharmacy, Department of Biomedical Sciences, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Pharmacology & Therapeutics (2002), 93(2-3), 145-157
CODEN: PHTHDT; ISSN: 0163-7258
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Protein kinases play critical roles in signal transduction pathways by transmitting extracellular signals across the cell membrane to distant locations in the cytoplasm and the nucleus. The development of protein kinase inhibitors has been hindered by the broad overlapping substrate specificities exhibited by these enzymes. The design of bisubstrate analog inhibitors could provide for the enhancement of specificity and potency in protein kinase inhibition. Bisubstrate analog inhibitors form a special group of protein kinase inhibitors that mimic two natural substrates/ligands and that simultaneously associate with two regions of given kinases. Most bisubstrate analogs have been designed to mimic the phosphate donor (ATP) and the acceptor components (Ser-, Thr-, or Tyr-containing peptides). Recent studies have emphasized the importance of maintaining a specific distance between these two components to achieve potent inhibition. In this review, we present a discussion of the methods for designing protein kinase inhibitors by mechanism-based approaches. Emphasis is given to bivalent approaches, with an interpretation of what has been learned from more and less successful examples. Future challenges in this area are also highlighted.
REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 34 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:417366 HCAPLUS
DOCUMENT NUMBER: 137:212726
TITLE: Development of photo-crosslinking reagents for protein kinase-substrate interactions
AUTHOR(S): **Parang, Keykavous**; Kohn, Jeffrey A.; Saldanha, S. Adrian; Cole, Philip A.
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: FEBS Letters (2002), 520(1-3), 156-160
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:212726
AB The identification of relevant protein kinase-protein substrate partners remains a serious challenge on a genome-wide scale. The design and synthesis of a photo-activatable nucleotide reagent to crosslink protein kinases with their substrates is described in which an azido group is appended to the γ-phosphoryl and purine moieties of ATP. In the absence of UV, compds. of this class were shown to act as competitive inhibitors vs. ATP and non-competitive inhibitors vs. peptide substrate for the protein tyrosine kinase Csk, suggesting that they can form a ternary complex with kinase and protein substrate. In vitro expts. with protein kinases indicate the bifunctional reagent can induce covalent protein-protein crosslinking that is dependent on UV irradiation That significant kinase-substrate crosslinking occurs is suggested by the fact that this crosslinking is competitively inhibited by ATP. The crosslinked adducts can be readily cleaved by phosphodiesterase which supports the model for crosslinking and provides a simple method to deconvolute the linked protein partners.
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 35 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:303593 HCAPLUS
DOCUMENT NUMBER: 137:150183
TITLE: Anti-HIV Design
AUTHOR(S): **Parang, Keykavous**; Editor
CORPORATE SOURCE: Neth.
SOURCE: (2002) Publisher: (Bentham Science Publishers: Hilversum, Neth.), 107 pp.
DOCUMENT TYPE: Book
LANGUAGE: English
AB Unavailable

L2 ANSWER 36 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:298454 HCAPLUS
TITLE: Preface
AUTHOR(S): **Parang, Keykavous**
CORPORATE SOURCE: Department of Biomedical Sciences College of Pharmacy, University of Rhode Island, Kingston, RI, 02881, USA
SOURCE: Current Pharmaceutical Design (2002), 8(8), NO pp.given
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; Miscellaneous
LANGUAGE: English

AB Unavailable

L2 ANSWER 37 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:713377 HCAPLUS
DOCUMENT NUMBER: 135:253738
TITLE: Bisubstrate inhibitors of kinases
INVENTOR(S): Courtney, Aliya; Cole, Philip A.; **Parang, Keykavous**; Abloogu, Ararat; Kohanski, Ron
PATENT ASSIGNEE(S): Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001070770	A2	20010927	WO 2001-US8886	20010321
WO 2001070770	A3	20020704		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002031820	A1	20020314	US 2001-811870	20010321
PRIORITY APPLN. INFO.:			US 2000-190799P	P 20000321

AB Protein kinase inhibitors have applications as anti-cancer therapeutic agents and biol. tools in cell signalling. Potent and selective bisubstrate inhibitors for the insulin receptor tyrosine kinase are based on a phosphoryl transfer mechanism involving a dissociative transition state. One such inhibitor is synthesized by linking ATPγS to a peptide substrate analog via a two-carbon spacer. The compound is a high-affinity competitive inhibitor against both nucleotide and peptide substrate and shows a slow off-rate. A crystal structure of this inhibitor bound to the tyrosine kinase domain of the insulin receptor confirms the key design features inspired by a dissociative transition state, and reveal that the linker takes part in the octahedral coordination of an active site Mg2+ ion. A Kemptide-ATPγS compound was also prepared This compound was an inhibitor of protein kinase A.

L2 ANSWER 38 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:37882 HCAPLUS
DOCUMENT NUMBER: 134:218831
TITLE: Mechanism-based design of a protein kinase inhibitor
AUTHOR(S): **Parang, Keykavous**; Till, Jeffrey H.; Ablooglu, Ararat J.; Kohanski, Ronald A.; Hubbard, Stevan R.; Cole, Philip A.
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Nature Structural Biology (2001), 8(1), 37-41
CODEN: NSBIEW; ISSN: 1072-8368
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Protein kinase inhibitors have applications as anticancer therapeutic agents and biol. tools in cell signaling. Based on a phosphoryl transfer mechanism involving a dissociative transition state, a potent and selective bisubstrate inhibitor for the insulin receptor tyrosine kinase was synthesized by linking ATPγS to a peptide substrate analog via a two-carbon spacer. The compound was a high affinity competitive inhibitor against both nucleotide and peptide substrates and showed a slow off-rate. A crystal structure of this inhibitor bound to the tyrosine kinase domain of the insulin receptor confirmed the key design features inspired by a dissociative transition state, and revealed that the linker takes part in the octahedral coordination of an active site Mg2+. These studies suggest a general strategy for the development of selective protein kinase inhibitors.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 39 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:6627 HCAPLUS
DOCUMENT NUMBER: 134:178758
TITLE: A Solid Phase Reagent for the Capture Phosphorylation of Carbohydrates and Nucleosides
AUTHOR(S): **Parang, Keykavous**; Fournier, Eric J.-L.; Hindsgaul, Ole
CORPORATE SOURCE: Department of Chemistry, University of Alberta, Edmonton, AB, T6G 2G2, Can.
SOURCE: Organic Letters (2001), 3(2), 307-309
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:178758

AB A 1% cross-linked divinylbenzene-polystyrene copolymer, containing cyanoethoxy N,N-diisopropylamine phosphine was prepared as a phosphitylating agent. The polymer-bound phosphitylated precursor was subjected to reaction with alcs. in the presence of 1H-tetrazole to produce the corresponding polymer-bound phosphite triesters. These were then oxidized with tert-Bu hydroperoxide to give the polymer-bound monophosphate triesters. Removal of cyanoethoxy on the resin with DBU followed by basic cleavage of the p-hydroxybenzyl linker products yielded monophosphate derivs.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 40 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:722331 HCAPLUS
DOCUMENT NUMBER: 134:53060
TITLE: Probing the catalytic mechanism of the insulin receptor kinase with a tetrafluorotyrosine-containing peptide substrate
AUTHOR(S): Ablooglu, Ararat J.; Till, Jeffrey H.; Kim, Kyonghee; **Parang, Keykavous**; Cole, Philip A.; Hubbard, Stevan R.; Kohanski, Ronald A.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Journal of Biological Chemistry (2000), 275(39), 30394-30398
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The interaction of a synthetic tetrafluorotyrosyl peptide substrate with the activated tyrosine kinase domain of the insulin receptor was studied by steady-state kinetics and x-ray crystallog. The pH-rate profiles indicate that the neutral phenol, rather than the chemical more reactive phenoxide ion, is required for enzyme-catalyzed phosphorylation. The pKa of the tetrafluorotyrosyl hydroxyl is elevated 2 pH units on the enzyme compared with solution, whereas the phenoxide anion species behaves as a weak competitive inhibitor of the tyrosine kinase. A structure of the binary enzyme-substrate complex shows the tetrafluorotyrosyl OH group at hydrogen bonding distances from the side chains of Asp1132 and Arg1136, consistent with elevation of the pKa. These findings strongly support a reaction mechanism favoring a dissociative transition state.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 41 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:678356 HCAPLUS

DOCUMENT NUMBER: 133:358790

TITLE: Novel approaches for designing 5'-O-ester prodrugs of 3'-Azido-2',3'-dideoxythymidine (AZT)

AUTHOR(S): **Parang, Keykavous**; Wiebe, Leonard I.; Knaus, Edward E.

CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, School of Medicine, Johns Hopkins University, Baltimore, MD, 21205-2185, USA

SOURCE: Current Medicinal Chemistry (2000), 7(10), 995-1039
CODEN: CMCHE7; ISSN: 0929-8673

PUBLISHER: Bentham Science Publishers

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review with 272 refs. 3'-Azido-2',3'-dideoxythymidine (AZT, 1, zidovudine, Retrovir) is used to treat patients with human immunodeficiency virus (HIV) infection. AZT, after conversion to AZT-5'-triphosphate (AZT-TP) by cellular enzymes, inhibits HIV-reverse transcriptase (HIV-RT). The major clin. limitations of AZT are due to clin. toxicities that include bone marrow suppression, hepatic abnormalities and myopathy, absolute dependence on host cell kinase-mediated activation which leads to low activity, limited brain uptake, a short half-life of about one hour in plasma that dictates frequent administration to maintain therapeutic drug levels, low potential for metabolic activation and/or high susceptibility to catabolism, and the rapid development of resistance by HIV-1. These limitations have prompted the development of strategies for designing prodrugs of AZT. A variety of 5'-O-substituted prodrugs of AZT constitute the subject of this review. The drug-design rationale on which these approaches are based is that the ester conjugate will be converted by hydrolysis and/or enzymic cleavage to AZT or its 5'-monophosphate (AZT-MP). Most prodrug derivs. of AZT have been prepared by derivatization of AZT at its 5'-O position to provide two prominent classes of compds. that encompass: (A) 5'-O-carboxylic esters derived from (1) cyclic 5'-O-carboxylic acids such as steroidal 17β-carboxylic acids, 1-adamantanecarboxylic acid, bicyclam carboxylic acid derivs., O-acetylsalicylic acid, and carbohydrate derivs., (2) amino acids, (3) 1,4-dihydro-1-methyl-3-pyridinylcarboxylic acid, (4) aliphatic fatty acid analogs such as myristic acid containing a heteroatom, or without a heteroatom such as stearic acid, and (5) long chain polyunsatd. fatty acid analogs such as retinoic acid, and (B) masked phosphates such as (1) phosphodiesters that include monoalkyl or monoaryl phosphate, carbohydrate, ether lipid, ester lipid, and foscarnet derivs., (2) a variety of phosphotriesters that include dialkylphosphotriesters,

diarylphosphotriesters, glycolate and lactate phosphotriesters, phosphotriester approaches using simultaneous enzymic and chemical hydrolysis of bis(4-acyloxybenzyl) esters, bis(S-acyl-2-thioethyl) (SATE) esters, cyclosaligenyl prodrugs, glycosyl phosphotriesters, and steroidal phosphotriesters, (3) phosphoramidate derivs., (4) dinucleoside phosphate derivs. that possess a second anti-HIV moiety such as AZT-P-ddA, AZT-P-ddI, AZTP2AZT, AZTP2ACV, and (5) 5'-hydrogen phosphonate and 5'-methylene phosphonate derivs. of AZT. In these prodrugs, the conjugating moiety is linked to AZT via a 5'-O-ester or 5'-O-phosphate group. 5'-O-Substituted AZT prodrugs have been designed with the objectives of improving anti-HIV activity, enhancing blood-brain barrier penetration, modifying pharmacokinetic properties to increase plasma half-life and improving drug delivery with respect to site-specific targeting or drug localization. Bypassing the first phosphorylation step, regulating transport and conferring sustained release of AZT prolong its duration of action, decrease toxicity and improve patient acceptability. The properties of these prodrugs and their anti-HIV activities are now reviewed.

REFERENCE COUNT: 272 THERE ARE 272 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 42 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:454823 HCAPLUS
DOCUMENT NUMBER: 133:219288
TITLE: Tyrosine analogues as alternative substrates for protein tyrosine kinase Csk: Insights into substrate selectivity and catalytic mechanism
AUTHOR(S): Kim, K.; **Parang, K.**; Lau, O. D.; Cole, P. A.
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Bioorganic & Medicinal Chemistry (2000), 8(6), 1263-1268
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Protein tyrosine kinases are critical enzymes in cell signal transduction but relatively little is known about the mol. recognition of the tyrosine substrate by these enzymes. Details of tyrosine substrate specificity within the context of a short peptide were investigated for protein tyrosine kinase Csk. It was found that aryl ring functional group substitutions the size of Me group or smaller were generally well tolerated by the protein tyrosine kinase Csk whereas larger groups caused a decline in substrate efficiency. Extension of the phenol from the peptide backbone by a single methylene was acceptable for phosphorylation whereas removal of a methylene nearly abolished reactivity. Only the L-tyrosine derivative was processed. A neg. charge ortho to the phenol hydroxyl was incompatible with substrate reactivity, consistent with previous pH rate profiles which indicated the importance of the neutral phenol. Overall, these studies confirmed the interpretation of a previous linear free energy relationship anal. which suggested that the enzyme followed a dissociative transition state mechanism.

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 43 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:332295 HCAPLUS
TITLE: Solid-phase strategy in the monophosphorylation of

carbohydrates and nucleosides.
AUTHOR(S): **Parang, Keykavous**; Fournier, Eric J-L.; Hindsgaul, Ole
CORPORATE SOURCE: Dept. of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), ORGN-170. American Chemical Society: Washington, D. C. CODEN: 69CLAC
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB A novel solid-phase assisted strategy for the regio- and stereoselective monophosphorylation of carbohydrates and nucleosides has been developed. Phosphorylation using solid-phase offers the advantages of facile isolation and the recovery of monophosphorylated products. A 1% crosslinked divinylbenzene-polystyrene copolymer, containing cyanoethoxy N,N-diisopropylamine phosphine was prepared as a phosphite donor. To demonstrate the utility and specificity of a solid-phase monophosphorylation system, the polymer-bound phosphorylated precursor was subjected to reactions with 1,2:3,4-di-O-isopropylidene-D-galactopyranose, n-octyl-β-D-glucopyranoside, D-galactose pentaacetate and uridine in the presence of 1-H-tetrazole to give the appropriate polymer-bound phosphite triesters. The resulting polymer-bound phosphite triesters were then oxidized with tert-Bu hydroperoxide to give the polymer-bound monophosphate triesters of the corresponding compds. The deprotection of cyanoethoxy with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) followed by basic cleavage cleavage from the resin yielded 1,2:3,4-di-O-isopropylidene-D-galactopyranosyl-6-phosphate, n-octyl-β-D-glucopyranosyl-6-phosphate, α-D-galactopyranosyl 1-phosphate and uridine-5'-monophosphate, resp.

L2 ANSWER 44 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:327119 HCAPLUS
TITLE: Substrate selectivity of unnatural tyrosine derivatives for protein tyrosine kinase csk.
AUTHOR(S): Kim, Kyonghee; **Parang, Keykavous**; Lau, Ontario D.; Cole, Philip A.
CORPORATE SOURCE: Dept. of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), BIOL-078. American Chemical Society: Washington, D. C. CODEN: 69CLAC
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Protein tyrosine kinases are critical enzymes in cell signal transduction. Details of tyrosine substrate specificity were investigated including features of charge, steric bulk, stereochem., aryl displacement from peptide backbone and hydrogen bonding. For example, a neg. charge ortho to phenol hydroxyl was incompatible with substrate reactivity, consistent with previous pH rate profiles which indicated the importance of the neutral phenol. Overall, these studies confirm the interpretation of a previous linear free energy relationship anal. which suggested that the enzyme follows a dissociative transition state mechanism.

L2 ANSWER 45 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:506025 HCAPLUS
DOCUMENT NUMBER: 132:87779

TITLE: In vitro anti-hepatitis B virus activities of 5'-O-myristoyl analogue derivatives of 3'-fluoro-2',3'-dideoxythymidine (FLT) and 3'-azido-2',3'-dideoxythymidine (AZT)
AUTHOR(S): **Parang, Keykavous**; Wiebe, Leonard I.; Knaus, Edward E.
CORPORATE SOURCE: Fac. Pharmacy and Pharmaceutical Sciences, Univ. Alberta, Edmonton, AB, T6G 2N8, Can.
SOURCE: Journal of Pharmacy & Pharmaceutical Sciences [Electronic Publication] (1998), 1(3), 108-114
CODEN: JPPSFY; ISSN: 1482-1826
PUBLISHER: Canadian Society for Pharmaceutical Sciences
DOCUMENT TYPE: Journal; (online computer file)
LANGUAGE: English

AB The objective of this study was to evaluate a dual action prodrug concept wherein an unnatural myristic acid analog is coupled via an ester moiety to the 5'-position of FLT or AZT. Subsequent intracellular cleavage of the prodrug ester would simultaneously release FLT or AZT that could inhibit reverse transcriptase (RT), and the myristic acid analog that could inhibit myristoyl-CoA:protein N-myristoyltransferase (NMT). Cytotoxicity (2.2.15 cell culture), and anti-hepatitis B activity of 5'-O-myristoyl analog prodrug derivs. of FLT and AZT (2-8) were evaluated in vitro using human liver hepatitis B virus (HBV) producing 2.2.15 cell lines. The 5'-O-(12-methoxydodecanoyl) ester derivs. of AZT (2, EC50 = 2.7 ± 0.3 μM; CC50 = 727 ± 19 μM) and FLT (4, EC50 = 2.8 ± 0.3 μM; CC50 = 186 ± 20 μM) were the most effective anti-hepatitis B virus (anti-HBV) compds. of this series in a replication assay. In the series of 5'-O-myristic acid analog ester prodrug derivs. of FLT, the relative anti-HBV potency order was MeO(CH2)11CO2- > N3(CH2)11CO2- and Br(CH2)11CO2- > EtS(CH2)8CO2-(n = 10 or 11) > Me(CH2)12CO2- (myristoyl). The in vitro data suggest that the 5'-O-myristoyl analog prodrug concept offers a potential drug design approach to design dual acting antiviral agents, with superior pharmacokinetic, biodistribution, reduced cytotoxicity and/or increased efficacy. In this regard, the 5'-O-(12-methoxydodecanoyl) prodrug ester of 3'-thia-3'-deoxythymidine (3TC) may offer the greatest potential for the treatment of HBV infection.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 46 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:681024 HCAPLUS
DOCUMENT NUMBER: 130:60568
TITLE: Pharmacokinetics and tissue distribution of (±)-3'-azido-2',3'-dideoxy-5'-O-(2-bromomyristoyl)thymidine, a prodrug of 3'-azido-2',3'-dideoxythymidine (AZT) in mice
AUTHOR(S): **Parang, Keykavous**; Wiebe, Leonard I.; Knaus, Edward E.
CORPORATE SOURCE: Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, T6G 2N8, Can.
SOURCE: Journal of Pharmacy and Pharmacology (1998), 50(9), 989-996
CODEN: JPPMAB; ISSN: 0022-3573
PUBLISHER: Royal Pharmaceutical Society of Great Britain
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The in-vivo biodistribution and pharmacokinetics in mice of 3'-azido-2',3'-dideoxythymidine (AZT), 2-bromomyristic acid and their common prodrug, (±)-3'-azido-2',3'-dideoxy-5'-O-(2-

bromomyristoyl)thymidine (I) are reported. The objectives of the work were to enhance the anti-human immunodeficiency virus and anti-fungal effects of AZT and 2-bromomyristic acid by improving their delivery to the brain and liver. The pharmacokinetics of AZT (βt1/2 (elimination, or beta-phase, half-life) = 112.5 min; AUC (area under the plot of concentration against time) = 29.1 ± 2.9 μmol g-1 min; CL (blood clearance) = 10.5 ± 1.1 mL min-1 kg-1) and its ester prodrug (I, βt1/2 = 428.5 min; AUC = 17.3 ± 4.7 μmol g-1 min; CL = 17.6 ± 4.8 mL min-1 kg-1) were compared after i.v. injection of equimolar doses (0.3 mmol kg-1) via the tail vein of Balb/c mice (25-30 g). The prodrug was rapidly converted to AZT in-vivo, but plasma levels of AZT (peak concentration 0.17 μmol g-1) and AUC (12.3 μmol min g-1) were lower than observed after AZT administration (peak concentration 0.36 μmol g-1; AUC 29.1 μmol min g-1). The prodrug also accumulated rapidly in the liver immediately after injection, resulting in higher concns. of AZT than observed after administration of AZT itself (resp. peak concns. 1.11 and 0.81 μmol g-1; resp. AUCs 42.5 and 12.7 μmol min g-1). Compared with doses of AZT itself, I also led to significantly higher brain concentration of AZT (25.7 compared with 9.8 nmol g-1) and AUCs (2.8 compared with 1.4 μmol min g-1). At the doses used in this study the antifungal agent 2-bromomyristic acid was measurable in plasma and brain within only 2 min of injection. Hepatic concns. of 2-bromomyristic acid were higher for at least 2 h after dosing with 3 than after dosing with the acid itself. In summary, comparative biodistribution studies of AZT and its prodrug showed that the prodrug led to higher concns. of AZT in the brain and liver. Although the prodrug did not result in measurably different concns. of 2-bromomyristic acid in the blood and brain, it did lead to levels in the liver which were higher than those achieved by dosing with the acid itself.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 47 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:529727 HCAPLUS
TITLE: In vitro anti-hepatitis B virus activities of 5'-O-myristoyl analog derivatives of 3'-fluoro-2',3'-dideoxythymidine (FLT) and 3'-azido-2',3'-dideoxythymidine (AZT).
AUTHOR(S): **Parang, K.**; Wiebe, L. I.; Knaus, E. E.; Huang, J.-S.; Tyrrell, D. L.
CORPORATE SOURCE: Department Chemistry, University Alberta, Edmonton, AB, T6G 2G2, Can.
SOURCE: Book of Abstracts, 216th ACS National Meeting, Boston, August 23-27 (1998), MEDI-242. American Chemical Society: Washington, D. C.
CODEN: 66KYA2
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Cytotoxicity and anti-hepatitis B activity of 5'-O-myristoyl analog prodrug derivs. of FLT and AZT were evaluated in vitro in 2.2.15 cells. The 5'-O-(12-methoxydodecanoyl)ester derivs. of AZT (EC50 = 2.7 ± 0.3 μM; CC50 = 727 ± 19 μM) and FLT (EC50 = 2.8 ± 0.3 μM; CC50 = 186 ± 20 μM) were the most effective anti-hepatitis B virus (anti-HBV) compds. of this series in a replication assay.

L2 ANSWER 48 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:529652 HCAPLUS
TITLE: Novel methodologies for carbohydrate sulfation.
AUTHOR(S): **Parang, K.**; Hindsgaul, O.
CORPORATE SOURCE: Department Chemistry, University Alberta, Edmonton,

AB, T6G 2G2, Can.
SOURCE: Book of Abstracts, 216th ACS National Meeting, Boston, August 23-27 (1998), MEDI-166. American Chemical Society: Washington, D. C.
CODEN: 66KYA2
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Crucial biol. roles for sulfated carbohydrate polymers, most notably heparin sulfate, chondroitin sulfate and tetrasaccharide sulfo-sialyl-LeX have long been recognized. The chemical required to synthesize this increasingly important class of mols. has not kept pace with the demands for structurally well defined inhibitors of the adhesion between the target protein receptors and the sulfated sugars. A new method has been developed for sulfation of some carbohydrates using derivs. of 2-hydroxy or 2-aminobenzyl alc. and sulfuryldiimidazole in an inert condition. For example, diacetone glucose was sulfated using 2-(α-hydroxyisopropyl)phenol and sulfuryldiimidazole in DMF to yield diacetone glucose 3-sulfate in 47% yield. This method may be used to develop a solid-phase technique for monosulfation of carbohydrate by immobilizing the sulfating agent on a highly rigid polystyrene matrix.

L2 ANSWER 49 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:513188 HCAPLUS
DOCUMENT NUMBER: 129:239454
TITLE: Synthesis, in vitro anti-human immunodeficiency virus structure-activity relationships and biological stability of 5'-O-myristoyl analog derivatives of 3'-azido-2',3'-dideoxythymidine (AZT) as potential prodrugs
AUTHOR(S): **Parang, K.**; Wiebe, L. I.; Knaus, E. E.
CORPORATE SOURCE: Fac. Pharm. Pharm. Sci., Univ. Alberta, Edmonton, AB, T6G 2N8, Can.
SOURCE: Antiviral Chemistry & Chemotherapy (1998), 9(4), 311-323
CODEN: ACCHEH; ISSN: 0956-3202
PUBLISHER: International Medical Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 5'-O-Myristoyl analog derivs. of 3'-azido-2',3'-dideoxythymidine (AZT), designed as potential double-barrelled prodrugs to AZT and the myristic acid analogs, were synthesized. Their ability to protect CEM cells against human immunodeficiency virus (HIV)-induced cytopathogenicity was determined and structure-activity paradigms were developed. 3'-Azido-2',3'-dideoxy-5'-O-(4-oxatetradecanoyl)thymidine (EC50=1.4 nM) and 3'-azido-2',3'-deoxy-5'-O-(12-bromododecanoyl)thymidine (EC50=3.2 nM) were the most effective anti-HIV-1 agents, relative to AZT (EC50=10 nM). These myristoyl analog derivs. were more lipophilic (calculated log P=4.5-8.1 range) than the parent compound AZT (log P=0.06), and a linear correlation between their log P and HPLC log retention times was observed The ester cleavage half-lives (t1/2) for esters upon in vitro incubation with porcine liver esterase, rat plasma or rat brain homogenate was dependent on the steric bulk, and electroneg. inductive effect of the α-substituent (H, Br, F), of the 5'-O-myristoyl analog moiety. 3'-Azido-2',3'-dideoxy-5'-O-(11-(4-iodophenoxy) undecanoyl)-thymidine exhibited t1/2 values of 80.4, 3.7 and 150.0 min upon incubation with porcine liver esterase, rat plasma and rat brain homogenate, resp.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 50 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1998:329096 HCAPLUS
DOCUMENT NUMBER: 129:54523
TITLE: Synthesis, in vitro anti-HIV activity, and biological stability of 5'-O-myristoyl analog derivatives of 3'-fluoro-2',3'-dideoxythymidine (FLT) as potential bifunctional prodrugs of FLT
AUTHOR(S): **Parang, Keykavous**; Knaus, Edward E.; Wiebe, Leonard I.
CORPORATE SOURCE: Faculty of Pharmacy, University of Alberta, Edmonton, AB, T6G 2N8, Can.
SOURCE: Nucleosides & Nucleotides (1998), 17(6), 987-1008
CODEN: NUNUD5; ISSN: 0732-8311
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A group of 5'-O-myristoyl analog derivs. of FLT were evaluated as potential anti-HIV agents that were designed to serve as prodrugs to FLT. 3'-Fluoro-2',3'-dideoxy-5'-O-(12-methoxydodecanoyl)thymidine (EC50 = 3.8 nM) and 3'-fluoro-2',3'-dideoxy-5'-O-(12-azidododecanoyl)thymidine (EC50 = 2.8 nM) were the most effective anti-HIV-1 agents. There was a linear correlation between Log P and HPLC Log retention time for the 5'-O-FLT esters. The in vitro enzymic hydrolysis half-life (t1/2), among the group of esters in porcine liver esterase, rat plasma and rat brain homogenate was longer for 3'-fluoro-2',3'-dideoxy-5'-O-(myristoyl)thymidine, with t1/2 values of 20.3, 4.6 and 17.5 min, resp.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 51 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:217046 HCAPLUS
DOCUMENT NUMBER: 128:316947
TITLE: Evaluation of myristic acid analogs and 5'-o-ester prodrugs of thymidine (dthd), 3'-azido-3'-deoxythymidine (azt) and 3'-fluoro-3'-deoxythymidine (flt)
AUTHOR(S): **Parang, Keykavous**
CORPORATE SOURCE: Univ. of Alberta, Edmonton, AB, Can.
SOURCE: (1997) 288 pp. Avail.: UMI, Order No. DANQ23054 From: Diss. Abstr. Int., B 1998, 58(11), 5905
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable

L2 ANSWER 52 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:595314 HCAPLUS
DOCUMENT NUMBER: 127:272236
TITLE: Syntheses and biological evaluation of 5'-O-myristoyl derivatives of thymidine against human immunodeficiency virus
AUTHOR(S): **Parang, K.**; Wiebe, L. I.; Knaus, E. E.
CORPORATE SOURCE: Fac. Pharm. Pharm. Sci., Univ. Alberta, Edmonton, AB, Can.
SOURCE: Antiviral Chemistry & Chemotherapy (1997), 8(5), 417-427
CODEN: ACCHEH; ISSN: 0956-3202
PUBLISHER: International Medical Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of 5'-O-acyl derivs. of thymidine (dThd) were prepared by direct acylation of thymidine using the Mitsunobu reaction Further reaction of

the bromo analogs with sodium azide gave azido ester analogs. Anti-human immunodeficiency virus type 1 (HIV-1) activities were determined against HIV-infected T4 lymphocytes. 5'-O-(12-Azidododecanoyl)thymidine exhibited moderate activity (EC50 4.6 μM) against HIV-infected T4 lymphocytes. 5'-O-(2-Bromotetradecanoyl)thymidine was found to be the most stable ester (t1/2 15.3 min) to hydrolysis by porcine liver esterase in vitro. Partition coeffs. (P) in n-octanol-phosphate buffer were determined (log10 P 3.96-6.53) using the PALLAS program. Anti-HIV structure-activity data suggest that the exptl. partition coefficient should be in the log10 P 4.6-4.8 range for optimum anti-HIV activity. The structures of these thymidine analogs were optimized using mol. mechanics (MM+ force field) and semi-empirical quantum mechanics PM3 calcns. The moderately active compds. adopted a similar C-2' endo sugar conformation and exhibited similar energies for the lowest energy conformer. A quant. structure-activity relationship (QSAR) regression equation was developed, based on the optimized structures and anti-HIV data using the SciQSAR program, which showed that log P was a determinant of anti-HIV activity.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

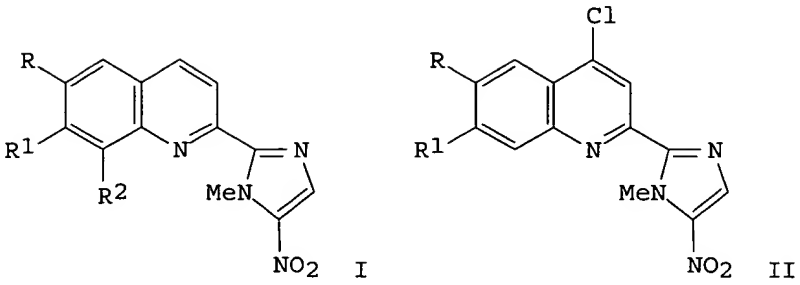
L2 ANSWER 53 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:395287 HCAPLUS
DOCUMENT NUMBER: 127:90130
TITLE: In vitro antiviral activities of myristic acid analogs against human immunodeficiency and hepatitis B viruses
AUTHOR(S): **Parang, Keykavous**; Wiebe, Leonard I.; Knaus, Edward E.; Huang, Jyy-Shiang; Tyrrell, David L.; Csizmadia, Ferenc
CORPORATE SOURCE: Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, AB, T6G 2N8, Can.
SOURCE: Antiviral Research (1997), 34(3), 75-90
CODEN: ARSRDR; ISSN: 0166-3542
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A group of myristic acid analogs, designed as alternative substrates for N-myristoyltransferase (NMT), were evaluated against human immunodeficiency virus (HIV), hepatitis B virus (HBV) and duck hepatitis B virus (DHBV) in vitro. Antiviral potency was increased when S or O was substituted for -CH2- in myristic acid and selectivity was affected by the presence and position of the heteroatoms and Ph groups. A correlation was established among anti-HIV activity, Log P and Log D7.4 and between anti-HIV activity and carbonyl-heteroatom interat. distances in the myristoyl analogs. 12-Thioethyldodecanoic acid was moderately active (EC50 = 9.37 μM) against HIV-infected T4-lymphocytes (CEM-SS cell line), and it exhibited in vitro activity (Ec50 = 17.8 μM) against HBV-producing 2.2.15 cell cultures derived from a human hepatoblastoma cell line (Hep G2). 12-Methoxydodecanoic acid exhibited in vitro activity (EC50 = 20-30 μM) against hepatitis B in the HBV DNA-transfected 2.2.15 cell line. At a concentration of 10 μg/mL, none of the fatty acids significantly inhibited the replication of DHBV in infected hepatocytes.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 54 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:20501 HCAPLUS
DOCUMENT NUMBER: 126:117733
TITLE: Synthesis and antifungal activities of myristic acid analogs
AUTHOR(S): **Parang, Keykavous**; Knaus, Edward E.; Wiebe,

Leonard I.; Sardari, Soroush; Daneshtalab, Mohsen; Csizmadia, Ferenc
CORPORATE SOURCE: Faculty Pharmacy Pharmaceutical Sciences, University Alberta, Edmonton, AB, T6G 2N8, Can.
SOURCE: Archiv der Pharmazie (Weinheim, Germany) (1996), 329(11), 475-482
CODEN: ARPMAS; ISSN: 0365-6233
PUBLISHER: VCH
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 126:117733
AB Myristic acid analogs were prepared and tested in vitro for activity against yeasts and filamentous fungi. Improved synthetic methods were developed for the synthesis of 12-fluorododecanoate and 12-chlorododecanoate. 12-Chloro-4-oxadodecanoate, 12-phenoxydodecanoate, and 11-(4-iodophenoxy)undecanoate were also prepared and tested. Several 2-halotetradecanoates including 2-bromotetradecanoate exhibited potent activity against C. albicans (MIC = 39 μM), C. neoformans (MIC = 20 μM), S. cerevisiae (MIC = 10 μM), and A. niger (MIC < 42 μM) in RPMI 1640 media.

L2 ANSWER 55 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:300828 HCAPLUS
DOCUMENT NUMBER: 122:160547
TITLE: Syntheses of 1-substituted 1,2,4-triazoles, imidazoles and benzimidazoles
AUTHOR(S): Sharifian, Abdollah; **Parang, Kaykavoos**; Zorrieh-Amirian, Hassan; Nazarinia, Mehrdad; Shafiee, Abbas
CORPORATE SOURCE: Dep. Chem., Med. Sci. Univ. Tehran, Tehran, Iran
SOURCE: Journal of Heterocyclic Chemistry (1994), 31(6), 1421-3
CODEN: JHTCAD; ISSN: 0022-152X
PUBLISHER: HeteroCorporation
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Substituted 2-phenylethyl-1,2,4-triazoles, 1-phenethylimidazoles and 1-phenethylbenzimidazoles were synthesized by dechlorination of the corresponding chloro derivative with tributyltin hydride in good yield. The reaction of substituted-2-phenethyl halide with 1H-1,2,4-triazoles, imidazoles and benzimidazoles gave a low yield. The yield was increased by the use of substituted-2-phenethyl p-toluenesulfonate.

L2 ANSWER 56 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:191631 HCAPLUS
DOCUMENT NUMBER: 118:191631
TITLE: Nitroimidazoles. X. Syntheses of substituted 2-(1-methyl-5-nitro-2-imidazolyl)quinolines
AUTHOR(S): Shafiee, A.; **Parang, K.**; Khazan, M.; Ghasemian, F.
CORPORATE SOURCE: Fac. Pharm., Med. Sci., Univ. Tehran, Tehran, Iran
SOURCE: Journal of Heterocyclic Chemistry (1992), 29(7), 1859-61
CODEN: JHTCAD; ISSN: 0022-152X
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I II

AB Reduction of 2-aminobenzaldehydes followed by cyclization with 2-acetyl-1-methyl-5-nitroimidazole under basic conditions afforded substituted 2-(1-methyl-5-nitro-2-imidazolyl)quinolinesI (R = H, F, Cl, Me, MeO; R1 = H, Cl; R2 = H, MeO). Oxidation of I (R = Cl, F, R1 = R2 = H; R = R2 = H, R1 = Cl) with H2O2 in HOAc afforded the N-oxide which was chlorinated with POCl3 to give addnl. title compds. II (R = H, Cl, F, R1 = H, Cl).

L2 ANSWER 57 OF 57 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:591759 HCAPLUS
DOCUMENT NUMBER: 117:191759
TITLE: Nitroimidazoles. IX. Synthesis of 2-acetyl-1-methyl-5-nitroimidazole
AUTHOR(S): Shafiee, A.; Pirouzzadeh, B.; Ghasemian, F.; **Parang, K.**
CORPORATE SOURCE: Coll. Pharm. Med. Sci., Univ. Tehran, Teheran, Iran
SOURCE: Journal of Heterocyclic Chemistry (1992), 29(4), 1021-3
CODEN: JHTCAD; ISSN: 0022-152X
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 117:191759
AB Manganese dioxide oxidation of 2-hydroxymethyl-1-methyl-5-nitroimidazole (6) gave 1-methyl-5-nitroimidazole-2-carboxaldehyde (7) in high yield. Reaction of diazomethane with 7 afforded the title compound 1 in low yield. Treatment of Et acid malonate with two equivalent of isopropylmagnesium bromide in THF and subsequent addition to 1-methyl-5-nitroimidazole-2-carbonylimidazolide (12) yielded Et (1-methyl-5-nitroimidazole-2-carbonyl)acetate (10) in 70% yield. Hydrolysis and decarboxylation of compound 10 gave the desired compound 1 in 97% yield.

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L2            57 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("PARANG K"/AU OR "PARANG
                 KAYKAVOOS"/AU OR "PARANG KEYKAVOUS"/AU)
L3             8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("ABLOOGLU ARARAT J"/AU OR
                 "ABLOOGLU ARARAT JAN"/AU OR "ABLOOGU ARARAT"/AU) NOT L2


=>
=>

=> d ibib abs l3 1-8

L3   ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:        2001:925443  HCAPLUS
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DOCUMENT NUMBER: 136:178085
TITLE: Multiple activation loop conformations and their regulatory properties in the insulin receptor's kinase domain
AUTHOR(S): **Ablooglu, Ararat J.**; Frankel, Mark; Rusinova, Elena; Ross, John B. Alexander; Kohanski, Ronald A.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Journal of Biological Chemistry (2001), 276(50), 46933-46940
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Low catalytic efficiency of protein kinases often results from intrasteric inhibition caused by the activation loop blocking the active site. In the insulin receptor's kinase domain, Asp-1161 and Tyr-1162 in the peptide substrate-like sequence of the unphosphorylated activation loop can interact with four invariant residues in the active site: Lys-1085, Asp-1132, Arg-1136, and Gln-1208. Contributions of these six residues to intrasteric inhibition were tested by mutagenesis, and the unphosphorylated kinase domains were characterized. The mutations Q1208S, K1085N, and Y1162F each relieved intrasteric inhibition, increasing catalytic efficiency but without changing the rate-limiting step of the reaction. The mutants R1136Q and D1132N were virtually inactive. Steric accessibility of the active site was ranked by relative changes in iodide quenching of intrinsic fluorescence, and A-loop conformation was ranked by limited tryptic cleavage. Together these ranked the openness of the active site cleft as R1136Q ≈ D1132N ≥ D1161A > Y1162F ≈ K1085N > Q1208S ≥ wild-type. These findings demonstrate the importance of specific invariant residues for intrasteric inhibition and show that diverse activation loop conformations can produce similar steady-state kinetic properties. This suggests a broader range of regulatory properties for the activation loop than expected from a simple off-vs.-on switch for kinase activation.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:852985 HCAPLUS
DOCUMENT NUMBER: 137:17065
TITLE: Regulation by autoinhibition in the insulin receptor kinase: mechanistic and mutagenic studies
AUTHOR(S): **Ablooglu, Ararat Jan**
CORPORATE SOURCE: Mount Sinai School of Medicine, New York Univ., New York, NY, USA
SOURCE: (2001) 207 pp. Avail.: UMI, Order No. DA9999466 From: Diss. Abstr. Int., B 2001, 61(12), 6447
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable

L3 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:447849 HCAPLUS
DOCUMENT NUMBER: 135:175627
TITLE: Intrasteric inhibition of ATP binding is not required to prevent unregulated autophosphorylation or

signaling by the insulin receptor
AUTHOR(S): Frankel, Mark; **Ablooglu, Ararat J.**; Leone, Joseph W.; Rusinova, Elena; Ross, J. B. Alexander; Heinrikson, Robert L.; Kohanski, Ronald A.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Molecular and Cellular Biology (2001), 21(13), 4197-4207
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Receptor tyrosine kinases may use intrasteric inhibition to suppress autophosphorylation prior to growth factor stimulation. To test this hypothesis the authors made an Asp1161Ala mutant in the activation loop that relieved intrasteric inhibition of the unphosphorylated insulin receptor (IR) and its recombinant cytoplasmic kinase domain (IRKD) without affecting the activated state. Solution studies with the unphosphorylated mutant IRKD demonstrated conformational changes and greater catalytic efficiency from a 10-fold increase in kcat and a 15-fold-lower Km ATP although Km peptide was unchanged. Kinetic parameters of the autophosphorylated mutant and wild-type kinase domains were virtually identical. The Asp1161Ala mutation increased the rate of in vitro autophosphorylation of the IRKD or IR at low ATP concns. and in the absence of insulin. However, saturation with ATP (for the IRKD) or the presence of insulin (for the IR) yielded equivalent rates of autophosphorylation for mutant vs. wild-type kinases. Despite a biochem. more active kinase domain, the mutant IR expressed in C2C12 myoblasts was not constitutively autophosphorylated. However, it displayed a 2.5-fold-lower 50% effective concentration for insulin stimulation of autophosphorylation and was dephosphorylated more slowly following withdrawal of insulin than wild-type IR. In tests of the regulation of the unphosphorylated basal state, these results demonstrate that neither intrasteric inhibition against ATP binding nor suppression of kinase activity is required to prevent premature autophosphorylation of the IR. Finally, the lower rate of dephosphorylation suggests invariant residues of the activation loop such as Asp 1161 may function at multiple junctures in cellular regulation of receptor tyrosine kinases.
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:267728 HCAPLUS
DOCUMENT NUMBER: 135:30699
TITLE: Crystallographic and solution studies of an activation loop mutant of the insulin receptor tyrosine kinase. Insights into kinase mechanism
AUTHOR(S): Till, Jeffrey H.; **Ablooglu, Ararat J.**; Frankel, Mark; Bishop, Steven M.; Kohanski, Ronald A.; Hubbard, Stevan R.
CORPORATE SOURCE: Skirball Institute of Biomolecular Medicine and Department of Pharmacology, New York University School of Medicine, New York, NY, 10016, USA
SOURCE: Journal of Biological Chemistry (2001), 276(13), 10049-10055
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The tyrosine kinase domain of the insulin receptor is subject to autoinhibition in the unphosphorylated basal state via steric interactions involving the activation loop. A mutation in the activation loop designed to relieve autoinhibition, Asp-1161 → Ala, substantially increases the ability of the unphosphorylated kinase to bind ATP. The crystal structure of this mutant in complex with an ATP analog has been determined at 2.4-Å resolution The structure shows that the active site is unobstructed, but the end of the activation loop is disordered and therefore the binding site for peptide substrates is not fully formed. In addition, Phe-1151 of the protein kinase-conserved DFG motif, at the beginning of the activation loop, hinders closure of the catalytic cleft and proper positioning of α-helix C for catalysis. These results, together with viscometric kinetic measurements, suggest that peptide substrate binding induces a reconfiguration of the unphosphorylated activation loop prior to the catalytic step. The crystallog. and solution studies provide new insights into the mechanism by which the activation loop controls phosphoryl transfer as catalyzed by the insulin receptor.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:887032 HCAPLUS

DOCUMENT NUMBER: 134:174807

TITLE: Activation of the Insulin Receptor's Kinase Domain Changes the Rate-Determining Step of Substrate Phosphorylation

AUTHOR(S): **Ablooglu, Ararat J.**; Kohanski, Ronald A.

CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, The Mount Sinai School of Medicine, New York, NY, 10029, USA

SOURCE: Biochemistry (2001), 40(2), 504-513
CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The insulin receptor and many other protein kinases are activated by relief of intrasteric inhibition that is regulated by reversible phosphorylation. The changes accompanying activation of the insulin receptor's kinase domain were analyzed using steady-state kinetics, viscometric anal., and equilibrium binding measurements. Peptide phosphorylation catalyzed by the unphosphorylated basal-state kinase is limited by a slow rate of the chemical step, and the activated enzyme is limited by product release rates. Underlying these changes were a 36-fold increase in the rate constant for the chemical step of the enzyme-catalyzed reaction, a 5-fold increase in the affinity for MgATP, and an 8-fold increase in the affinity for peptide substrate. This results in binding of substrates that is 2.2 kcal/mol more favorable and a free energy barrier for transition state formation that is lowered by 2.1 kcal/mol in the activated enzyme. Therefore, the change in conformational free energy inherent in the protein after autophosphorylation [Bishop, S. M., Ross, J. B. A., and Kohanski, R. A. (1999) Biochem. 38, 3079-3089] is equally distributed between formation of the substrate ternary complex and formation of the transition state complex.

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:709640 HCAPLUS

DOCUMENT NUMBER: 132:10355

TITLE: Conformational changes in the activation loop of the insulin receptor's kinase domain
AUTHOR(S): Frankel, Mark; Bishop, Steven M.; **Ablooglu, Ararat J.**; Han, Yuan-Ping; Kohanski, Ronald A.
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Protein Science (1999), 8(10), 2158-2165
CODEN: PRCIEI; ISSN: 0961-8368
PUBLISHER: Cambridge University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The low catalytic efficiency of basal-state protein kinases often depends on activation loop residues blocking substrate access to the catalytic cleft. Using the recombinant soluble form of the insulin receptor kinase domain (IRKD) in its unphosphorylated state, the activation loop conformation was analyzed by limited proteolysis. The rate of activation loop cleavage by trypsin was slow in the apo-IRKD. Bound MgADP and MgATP increased the cleavage rate with half-maximal effects observed at 0.4-0.9 mM nucleotide concentration AMP at concns. of ≤10 mM was not bound appreciably by the IRKD and had virtually no impact on activation loop cleavage. N-terminal and C-terminal core-flanking regions of IRKD had no statistically significant impact on the ligand-dependent or -independent activation loop cleavages. Furthermore, the core-flanking regions did not change the inherent conformational stability of the active site or the global stability of IRKD, as determined by guanidinium chloride-induced denaturation. These measurements indicated that the intrasterically inhibitory conformation encompassed ≥90% of the ligand-free basal state kinase. However, normal intracellular concns. of Mg-adenine nucleotides, which were in the millimolar range, would favor a basal-state conformation of the activation loop that was more accessible.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:475698 HCAPLUS
DOCUMENT NUMBER: 129:227372
TITLE: Partial Activation of the Insulin Receptor Kinase Domain by Juxtamembrane Autophosphorylation
AUTHOR(S): Cann, Aaron Darius; Bishop, Steven M.; **Ablooglu, Ararat J.**; Kohanski, Ronald A.
CORPORATE SOURCE: Department of Biochemistry, The Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Biochemistry (1998), 37(32), 11289-11300
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Increased enzymic activity of receptor tyrosine kinases occurs after trans-phosphorylation of one or two tyrosines in the activation loop, located near the catalytic cleft. Partial activation of the insulin receptor's kinase domain was observed at dilute concns. of kinase, suggesting that cis-autophosphorylation was occurring. Autophosphorylation during partial activation mapped to the juxtamembrane (JM) tyrosines and not to activation loop tyrosines. Furthermore, a double JM Tyr-to-Phe mutant kinase (JMY2F) did not undergo partial activation but catalyzed substrate phosphorylation at a very low rate. Steady-state kinetics of peptide phosphorylation were determined with and without JM autophosphorylation. The JMY2F mutant was used to prevent concurrent cis-autophosphorylation and therefore to approx. the basal state apoenzyme in the kinetic anal.

Partial activation was dominated by a decreased Michaelis constant for peptide substrate, from Km,PEP ≥ 2.5 mM in the basal state to 0.2 mM in the partially activated state; the Km,ATP remained virtually unchanged at .apprx.1 mM, and kcat increased from 180 to 600 min-1. The high Km,PEP suggests weak binding of peptide substrates to the apoenzyme. This was confirmed by Ki > 1 mM for peptide substrates used as inhibitors of JM autophosphorylation. The absence of comparably large changes in kcat and Km,ATP suggests that the JM region is primarily a strong barrier to the peptide entry step of trans-phosphorylation reactions. The JM region therefore functions as an intrasteric inhibitor in the basal state of the insulin receptor's kinase domain.

REFERENCE COUNT: 90 THERE ARE 90 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:257983 HCAPLUS
DOCUMENT NUMBER: 126:302279
TITLE: A Bacillus subtilis locus encoding several gene products affecting transport of cations
AUTHOR(S): Sturr, Michael G.; **Ablooglu, Ararat J.**; Krulwich, Terry A.
CORPORATE SOURCE: Dep. Biochem., Mount Sinai Sch. Med. CUNY, New York, NY, 10029, USA
SOURCE: Gene (1997), 188(1), 91-94
CODEN: GENED6; ISSN: 0378-1119
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A 3.6-kb DNA fragment from Bacillus subtilis was found to complement the K+ uptake-deficient Escherichia coli strain TK2420. Transformation with a pKLO61 plasmid harboring this fragment conferred the capacity to grow on a minimal medium containing only 10 mM K+. Insertional mutagenesis and subcloning identified a single gene responsible for the complementation. This gene coded for an apparent homolog of E. coli TrkA. Sequence anal. of the cloned region also revealed three addnl. open reading frames. These included: a gene encoding a homolog to the czcD gene product of Alcaligenes eutrophus, a lysR-type regulatory gene which was found to enhance Na+ resistance in E. coli NM81 (ΔnhaA) in a sep. complementation test, and an orfD with no significant similarity to sequences deposited in Genbank.

=> => d stat que
L2 57 SEA FILE=HCAPLUS ABB=ON PLU=ON ("PARANG K"/AU OR "PARANG KAYKAVOOS"/AU OR "PARANG KEYKAVOUS"/AU)
L3 8 SEA FILE=HCAPLUS ABB=ON PLU=ON ("ABLOOGLU ARARAT J"/AU OR "ABLOOGLU ARARAT JAN"/AU OR "ABLOOGU ARARAT"/AU) NOT L2
L4 45 SEA FILE=HCAPLUS ABB=ON PLU=ON ("KOHANSKI R"/AU OR "KOHANSKI R A"/AU OR "KOHANSKI RON"/AU OR "KOHANSKI RON A"/AU OR "KOHANSKI RONALD"/AU OR "KOHANSKI RONALD A"/AU) NOT (L2 OR L3)

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L4 ANSWER 1 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:103697 HCAPLUS
DOCUMENT NUMBER: 143:188336
TITLE: Biotinylation of proteins
AUTHOR(S): **Kohanski, Ronald A.**
CORPORATE SOURCE: The Johns Hopkins University, Baltimore, MD, USA

SOURCE: Encyclopedia of Biological Chemistry (2004), Volume 1, 179-181. Editor(s): Lennarz, William J.; Lane, M. Daniel. Elsevier Ltd.: Oxford, UK.
CODEN: 69GLBX; ISBN: 0-12-443710-9
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review. The biotinylation of proteins is the covalent coupling of biotin to an amino acid or carbohydrate moiety of the protein. Biotinylation occurs in a specific group of proteins known as carboxylases. These are enzymes that are important in several metabolic pathways, including amino acid metabolism, fatty acid biosynthesis, and gluconeogenesis. Each of these carboxylases is biotinylated on a single Lys residue through the action of a biotin-protein ligase, and are found in all organisms (bacteria, plants, and animals). Biotinylation of proteins is also done by in vitro chemical synthesis, whereby biotin can be covalently coupled to any reactive functional group on the protein, and is not necessarily restricted to a single amino acid residue.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:298522 HCAPLUS
DOCUMENT NUMBER: 139:98157
TITLE: Axons guided by insulin receptor in Drosophila visual system
AUTHOR(S): Song, Jianbo; Wu, Lingling; Chen, Zun; **Kohanski, Ronald A.**; Pick, Leslie
CORPORATE SOURCE: Brookdale Department for Molecular, Cell and Developmental Biology, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Science (Washington, DC, United States) (2003), 300(5618), 502-505
CODEN: SCIEAS; ISSN: 0036-8075
PUBLISHER: American Association for the Advancement of Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Insulin receptors are abundant in the central nervous system, but their roles remain elusive. Here we show that the insulin receptor functions in axon guidance. The Drosophila insulin receptor (DInR) is required for photoreceptor-cell (R-cell) axons to find their way from the retina to the brain during development of the visual system. DInR functions as a guidance receptor for the adapter protein Dock/Nck. This function is independent of Chico, the Drosophila insulin receptor substrate (IRS) homolog.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:963302 HCAPLUS
DOCUMENT NUMBER: 138:231872
TITLE: Dual mechanism of signal transducer and activator of transcription 5 activation by the insulin receptor
AUTHOR(S): Le, Maithao N.; **Kohanski, Ronald A.**; Wang, Lu-Hai; Sadowski, Henry B.
CORPORATE SOURCE: Department of Microbiology, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Molecular Endocrinology (2002), 16(12), 2764-2779
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Insulin stimulates signal transducer and activator of transcription 5 (Stat5) activation in insulin receptor (IR)-overexpressing cell lines and in insulin target tissues of mice. Stat5b and insulin receptor substrate 1 (IRS-1) interact with the same auto-phosphorylation site in the IR [phosphotyrosine (pY) 972] in yeast two-hybrid assays, and the IR phosphorylates Stat5b in vitro. These data suggest that Stat5 proteins might be recruited to, and phosphorylated by, the activated IR in vivo. Nevertheless, insulin activates Janus kinases (JAKs) in IR-overexpressing cell lines and in insulin target tissues. To determine whether Stat5 proteins must be recruited to the pY972LSA motif in the IR for insulin-stimulated activation in mammalian cells, the authors generated and tested a series of IR mutants. The L973R/A975D mutation abolishes the ability of the IR to induce Stat5 activation, whereas IRS-1 phosphorylation is unaffected. In contrast, the N969A/P970A mutation in the IR has no effect on Stat5 activation but significantly reduces IRS-1 phosphorylation. In coimmunopptn. assays, insulin-stimulated Stat5 activation correlates with Stat5 recruitment to the IR. The authors also find that insulin stimulates tyrosine phosphorylation of JAKs that are constitutively associated with the IR. Expression of dominant-neg. (DN) JAKs, the JAK inhibitor suppressor of cytokine signaling 1, or pretreatment with the JAK inhibitor, AG490, reduces, but does not eliminate, insulin-induced Stat5 activation. Expression of the appropriate pair of DN JAKs in each of the singly JAK-deficient cell lines further establishes a component of insulin-stimulated Stat5 activation that is JAK independent. This likely represents phosphorylation of Stat5 proteins by the IR, as the authors find that IR kinase domain phosphorylates Stat5b in vitro on Y699 as efficiently as JAK2. Increasing the concentration of Stat5 proteins in cells favors the direct phosphorylation of Stat5 by the IR kinase where the DN-JAK inhibition of insulin-stimulated Stat5 activation becomes insignificant. At physiol. levels of Stat5 however, the authors propose that JAKs and the IR both contribute to the insulin-induced phosphorylation of Stat5.

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2001:257061 HCAPLUS

DOCUMENT NUMBER: 135:71039

TITLE: A novel small molecule that directly sensitizes the insulin receptor in vitro and in vivo

AUTHOR(S): Manchem, Vara Prasad; Goldfine, Ira D.; **Kohanski, Ronald A.**; Cristobal, Cristina P.; Lum, Robert T.; Schow, Steven R.; Shi, Songyuan; Spevak, Wayne R.; Laborde, Edgardo; Toavs, Deborah K.; Villar, Hugo O.; Wick, Michael M.; Kozlowski, Michael R.

CORPORATE SOURCE: Telik, Inc., South San Francisco, CA, 94080, USA

SOURCE: Diabetes (2001), 50(4), 824-830
CODEN: DIAEAZ; ISSN: 0012-1797

PUBLISHER: American Diabetes Association

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Insulin resistance, an important feature of type 2 diabetes, is manifested as attenuated insulin receptor (IR) signaling in response to insulin binding. A drug that promotes the initiation of IR signaling by enhancing IR autophosphorylation should, therefore, be useful for treating type 2 diabetes. This report describes the effect of a small mol. IR sensitizer, TLK16998, on IR signaling. This compound activated the tyrosine kinase domain of the IR β-subunit at concns. of 1 μmol/l or less but had no effect on insulin binding to the IR α-subunit even at much higher

concns. TLK16998 alone had no effect on IR signaling in mouse 3T3-L1 adipocytes but, at concns. as low as 3.2 μmol/l, enhanced the effects of insulin on the phosphorylation of the IR β-subunit and IR substrate 1, and on the amount of phosphatidylinositol 3-kinase that co-immunopptd. with IRS-1. Phosphopeptide mapping revealed that the effect of TLK16998 on the IR was associated with increased tyrosine phosphorylation of the activation loop of the β-subunit tyrosine kinase domain. TLK16998 also increased the potency of insulin in stimulating 2-deoxy-D-glucose uptake in 3T3-L1 adipocytes, with a detectable effect at 8 μmol/l and a 10-fold increase at 40 μmol/l. In contrast, only small effects were observed on IGF-1-stimulated 2-deoxy-D-glucose uptake. In diabetic mice, TLK16998, at a dose of 10 mg/kg, lowered blood glucose levels for up to 6 h. These results suggest, therefore, that small nonpeptide mols. that directly sensitize the IR may be useful for treating type 2 diabetes.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:251038 HCAPLUS
DOCUMENT NUMBER: 133:2960
TITLE: Regulation of mOAT-mediated organic anion transport by okadaic acid and protein kinase C in LLC-PK1 cells
AUTHOR(S): You, Guofeng; Kuze, Kogo; **Kohanski, Ronald A.** ; Amsler, Kurt; Henderson, Scott
CORPORATE SOURCE: Department of Medicine, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Journal of Biological Chemistry (2000), 275(14), 10278-10284
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Organic anion transporters in the kidney proximal tubule play an essential role in eliminating a wide range of organic anions including endogenous compds., xenobiotics, and their metabolites, thereby preventing their potentially toxic effects within the body. We have previously cloned a cDNA encoding an organic anion transporter from mouse kidney (mOAT). In the present study, we assessed the potential for regulation of this transporter by heterologous expression of mOAT in the pig proximal tubule-like cell line, LLC-PK1. We report here that both protein phosphatase (PP1/PP2A) inhibitor, okadaic acid, and protein kinase C (PKC) activators down-regulate mOAT-mediated transport of para-aminohippuric acid (PAH), a prototypic organic anion, in a time- and concentration-dependent manner. However their mechanisms of action for this down-regulation are distinct. Okadaic acid modulated PAH transport, at least in part, through phosphorylation/dephosphorylation of mOAT; phosphoamino acid anal. indicated this phosphorylation occurs on serine. In contrast, PKC activation induced a decrease in the maximum transport velocity (Vmax) of PAH transport without direct phosphorylation of the transporter protein. Together these results provide the first demonstration that regulation of organic anion transport by mOAT is likely to be tightly controlled directly and indirectly by phosphatase PP1/PP2A and PKC. Our results also suggest that kinases other than PKC are involved in this process.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:725359 HCAPLUS

DOCUMENT NUMBER: 132:48369
TITLE: The promyelocytic leukemia zinc finger (PLZF) protein binds DNA in a high molecular weight complex associated with cdc2 kinase
AUTHOR(S): Ball, Helen J.; Melnick, Ari; Shaknovich, Rita; **Kohanski, Ronald A.**; Licht, Jonathan D.
CORPORATE SOURCE: Derald H. Ruttenberg Cancer Center, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Nucleic Acids Research (1999), 27(20), 4106-4113
CODEN: NARHAD; ISSN: 0305-1048
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A binding site selection from a CpG island library for the promyelocytic leukemia zinc finger protein (PLZF) identified two high affinity PLZF binding sites. These sequences also bound RARα/PLZF, a fusion protein formed in chromosomal translocation t(11;17)(q23;q21) associated with acute promyelocytic leukemia. PLZF bound DNA as a slowly migrating complex with an estimated mol. weight of 600 kDa whose formation was dependent on the POZ/dimerization domain of PLZF. The PLZF-DNA complex was unable to form in the presence of cdc2 antibodies. A PLZF-cdc2 interaction was further demonstrated by co-immunopptn. and a biotin-streptavidin pull-down assay. PLZF is a phosphoprotein and immunoppts. with a cdc2-like kinase activity. The PLZF-DNA complex was abolished with the addition of a phosphatase. These studies suggest that the activity of PLZF, a regulator of the cell cycle, may be modulated by cell cycle proteins. RARα/PLZF did not complex with cdc2, this potentially contributing to its aberrant transcriptional properties and potential role in leukemogenesis.
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:652960 HCAPLUS
DOCUMENT NUMBER: 131:348403
TITLE: Lysozyme degradation by the bovine multicatalytic proteinase complex (proteasome): Evidence for a nonprocessive mode of degradation
AUTHOR(S): Wang, Rong; Chait, Brian T.; Wolf, Imrey; **Kohanski, Ronald A.**; Cardozo, Christopher
CORPORATE SOURCE: Departments of Medicine Pharmacology and Biochemistry, The Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Biochemistry (1999), 38(44), 14573-14581
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The multicatalytic proteinase complex (MPC, proteasome) is composed of 28 subunits organized into four rings surrounding a water-filled canal. The catalytic centers face the inner canal confining protein substrates to an enclosed space. Exptl. findings obtained with MPC from archaebacteria suggest that degradation of proteins by the complex is processive and have led to the proposal that the lengths of the peptides formed during degradation depend on the distances between active sites in the catalytic chamber. To test whether these postulates are valid for the MPC from a higher organism, we examined the size distributions of products formed early vs. late in the course of protein degradation using reduced carboxamidomethylated lysozyme (RCM-lysozyme) and MPC from bovine spleen and pituitary. The

majority of final degradation products ranged in length from 6 to 20 amino acids without a clear predilection for peptides of a particular, uniform size. Our observations suggest that selection of cleavage sites is governed by the amino acid sequence specificity of the MPC catalytic sites rather than the distances between the active sites. Early in the course of degradation, peptides with masses between 5 and 10 kDa accumulated in more than 80-fold molar excess over the MPC, indicating dissociation of large, partially degraded intermediates. Initial cleavages occurred at distances between 10 and 44 amino acids from the N- or C-terminus of the mol. and often involved removal of a fragment from both the N- and C-termini of RCM-lysozyme. Our data indicate that degradation of proteins by MPCs from higher organisms involves a nonprocessive mechanism comprised of multiple, independent cleavages with dissociation of degradation intermediates. A general model for protein degradation by the MPC is discussed.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:109764 HCAPLUS
DOCUMENT NUMBER: 130:293210
TITLE: Autophosphorylation Dependent Destabilization of the Insulin Receptor Kinase Domain: Tryptophan-1175 Reports Changes in the Catalytic Cleft
AUTHOR(S): Bishop, Steven M.; Ross, J. B. Alexander; **Kohanski, Ronald A.**
CORPORATE SOURCE: Department of Biochemistry, The Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Biochemistry (1999), 38(10), 3079-3089
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Protein kinases are regulated by conformational or chemical changes which facilitate access of substrates to the active site and promote correct orientations of catalytically essential residues and water mols. The switch between basal and activated states of the insulin receptor's kinase domain (IRKD) results from autophosphorylation. We investigated the effects of IRKD autophosphorylation on the conformational stability by guanidine hydrochloride (GdnHCl) dependent denaturation and by iodide quenching of intrinsic fluorescence. Tryptophan residues of the recombinant soluble IRKD (residues R953-S1355) were excited at a λex of 295 nm, and emission spectra were analyzed for centroid (a characteristic of average polarity of the indole rings' environments) and integrated fluorescence intensity over the λem range of 310-420 nm. Denaturation profiles of both apo- and phospho-IRKD forms are complex with at least three distinct unfolding transitions. The first and last transitions were reversible and cooperative and had midpoints at 0.4 or 0.7 M GdnHCl and 2.4 or 2.7 M GdnHCl, resp.; transitions of phospho-IRKD occurred at lower GdnHCl concns. Calcns. of free energy of unfolding suggested a loss of .apprx.2.3 kcal/mol of stabilization for the first transition and .apprx.1.5 kcal/mol for the third transition. CD showed subtle changes in secondary structure over the first transition and global unfolding over the last transition. The first transition reports changes primarily in the local environment of W1175, which is near the catalytic loop and is conserved among protein tyrosine kinases. W1175 is also the dominant fluorophore of the native emission spectrum. Iodide quenching of W1175 was virtually undetectable in the apo-IRKD but significant in the phospho-IRKD, suggesting that W1175 exposure to small solutes is strongly dependent on the conformation of the activation loop. These studies

indicate that autophosphorylation, while exposing the catalytic center, also produces a conformer less stable than the apoenzyme.
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:509345 HCAPLUS
DOCUMENT NUMBER: 129:144864
TITLE: Modulators of insulin receptor activity, screening, and therapeutic use
INVENTOR(S): Kauvar, Lawrence M.; Sportsman, Richard; Villar, Hugo O.; Spevak, Wayne R.; **Kohanski, Ron A.**; Satyam, Apparao; Koehler, Ryan
PATENT ASSIGNEE(S): Terrapin Technologies, Inc., USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9832017	A2	19980723	WO 1998-US801	19980115
WO 9832017	A3	19990225		
W: AU, BA, CA, CU, GH, GM, GW, ID, JP, LC, SL, YU, ZW				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5830918	A	19981103	US 1997-784857	19970115
US 5851988	A	19981222	US 1997-784854	19970115
US 6329431	B1	20011211	US 1997-916088	19970821
CA 2278023	AA	19980723	CA 1998-2278023	19980115
AU 9860266	A1	19980807	AU 1998-60266	19980115
EP 960335	A2	19991201	EP 1998-903515	19980115
EP 960335	B1	20050525		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002512685	T2	20020423	JP 1998-534532	19980115
AT 296446	E	20050615	AT 1998-903515	19980115
US 2002016367	A1	20020207	US 2001-961179	20010921
US 2003078188	A1	20030424	US 2001-999762	20011025
AU 780473	B2	20050324	AU 2002-34362	20020416
AU 2002034362	A5	20020606		

PRIORITY APPLN. INFO.:	US 1997-784854	A	19970115
	US 1997-784855	A	19970115
	US 1997-784857	A	19970115
	US 1997-825269	A	19970327
	US 1997-916088	A	19970821
	WO 1998-US801	W	19980115
	US 1998-88507	B1	19980601

OTHER SOURCE(S): MARPAT 129:144864
AB Methods to identify compds. which have ≥1 characteristic selected from the group consisting of a composition that (a) modulates the kinase activity of insulin receptor; and/or (b) potentiates the insulin activation of insulin receptor; and/or (c) potentiates the stimulation by insulin of cellular glucose uptake; and/or (d) stimulates the uptake of glucose in cells displaying the insulin receptor; and/or (e) lowers blood glucose in diabetic subjects; and/or (f) stimulates IRS-1 phosphorylation; and/or (g) stimulates PI3 kinase activity; and/or (h) stimulates GLUT-4 translocation; are described. Successful substances having such characteristics alter the conformation of the two-lobed cytoplasmic kinase

domain or preferentially bind sites which have been identified as modulator binding sites in the insulin receptor β chain. Also, modulation of the activity of the insulin receptor, enhancement of glucose uptake by cells, and other effects significant in the control and management of diabetes are accomplished using [Ari(A)(R)mlinkeri]nAr(A)(R)m (Ar = aromatic moiety; A = proton-accepting substituent; R = non-interfering substituent; m = 0-2 n = 1-6; linker = CH2, N=N, CH=CH, NHCO, NHCONH or isostere thereof; when n = 1, ≥1 Ar must comprise ≥2 fused aromatic rings) (I). I can also be used for structure-activity studies to identify features responsible for the relevant activities.

L4 ANSWER 10 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:429428 HCAPLUS
DOCUMENT NUMBER: 129:185958
TITLE: Altered properties of the branched chain amino acid-preferring activity contribute to increased cleavages after branched chain residues by the "immunoproteasome"
AUTHOR(S): Cardozo, Christopher; **Kohanski, Ronald A.**
CORPORATE SOURCE: Departments of Medicine and Biochemistry, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Journal of Biological Chemistry (1998), 273(27), 16764-16770
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The multicatalytic proteinase complex (MPC, proteasome) is assembled from 14 nonidentical protein subunits. It expresses five distinct proteolytic activities, including a chymotrypsin-like activity, cleaving after hydrophobic residues, and a branched chain amino acid-preferring component (BrAAP), cleaving preferentially after branched chain residues. Exposure of cells to interferons leads to replacement of the X, Y, and Z subunits by the LMP2, LMP7, and MECL1 subunits. This immunoproteasome is critical to processing of certain antigens. The enzymic basis for enhanced antigen processing has not been determined To gain insight into this question, we examined sites and relative rates of cleavage of bonds in denatured, reduced, carboxy-amidomethylated lysozyme, a 129-amino acid protein, by MPC from bovine spleen, in which the X, Y, and Z subunits are replaced by LMP2, LMP7, and MECL1. We compared cleavages to those catalyzed by MPC from bovine pituitary, which contains only the X, Y, and Z subunits. We found marked increases in the rates and number of cleavages after branched chain residues in reduced, carboxyamidomethylated lysozyme by the spleen MPC. This was largely due to accelerated cleavages of bonds after a Φ-X-Br motif, where Φ is a hydrophobic residue, X is a small neutral or polar residue, and Br is a branched chain residue. Inhibitors with these structural properties were selective and potent inhibitors of the BrAAP activity of the spleen MPC. The above findings indicate that alterations in activity and substrate specificity of the BrAAP activity are important factors underlying the altered cleavages after hydrophobic residues associated with incorporation of interferon-inducible subunits. The potential relevance of the findings to antigen-processing functions of MPC is discussed.
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:350807 HCAPLUS

DOCUMENT NUMBER: 129:77533
TITLE: A binding site for multiple transcriptional activators in the fushi tarazu proximal enhancer is essential for gene expression in vivo
AUTHOR(S): Han, Wei; Yu, Yan; Su, Kai; **Kohanski, Ronald A.**; Pick, Leslie
CORPORATE SOURCE: Brookdale Center for Developmental and Molecular Biology, Mt. Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Molecular and Cellular Biology (1998), 18(6), 3384-3394
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The Drosophila homeobox gene fushi tarazu (ftz) is expressed in a highly dynamic striped pattern in early embryos. A key regulatory element that controls the ftz pattern is the ftz proximal enhancer, which mediates pos. autoregulation via multiple binding sites for the Ftz protein. In addition, the enhancer is necessary for stripe establishment prior to the onset of autoregulation. We previously identified nine binding sites for multiple Drosophila nuclear proteins in a core 323-bp region of the enhancer. Three of these nine sites interact with the same cohort of nuclear proteins in vitro. We showed previously that the nuclear receptor Ftz-F1 interacts with this repeated module. Here we purified addnl. proteins interacting with this module from Drosophila nuclear exts. Peptide sequences of the zinc finger protein Ttk and the transcription factor Adf-1 were obtained. While Ttk is thought to be a repressor of ftz stripes, we have shown that both Adf-1 and Ftz-F1 activate transcription in a binding site-dependent fashion. These two proteins are expressed ubiquitously at the time ftz is expressed in stripes, suggesting that either may activate striped expression alone or in combination with the Ftz protein. The roles of the nine nuclear factor binding sites were tested in vivo, by site-directed mutagenesis of individual and multiple sites. The three Ftz-F1-Adf-1-Ttk binding sites were found to be functionally redundant and essential for stripe expression in transgenic embryos. Thus, a biochem. anal. identified cis-acting regulatory modules that are required for gene expression in vivo. The finding of repeated binding sites for multiple nuclear proteins underscores the high degree of redundancy built into embryonic gene regulatory networks.
REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:686560 HCAPLUS
DOCUMENT NUMBER: 127:355530
TITLE: Phenylarsine oxide inhibits insulin activation of phosphatidylinositol 3'-kinase
AUTHOR(S): Han, Yuan-Ping; **Kohanski, R. A.**
CORPORATE SOURCE: The Department of Biochemistry, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Biochemical and Biophysical Research Communications (1997), 239(1), 316-321
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two early events downstream of insulin receptor autophosphorylation that are necessary for activation of glucose transport in adipocytes appear to be: (1) The tyrosine phosphorylation of insulin receptor substrate-1

(IRS-1) which (2) recruits and activates phosphatidylinositol 3'-kinase (PI3'-K). Phenylarsine oxide (PAO) has long been known to inhibit glucose transport, without inhibiting insulin receptor auto- or substrate phosphorylation. However, the PAO-sensitive site downstream of these early regulatory events has not been identified. Here we provide evidence that exposure of 3T3-L1 adipocytes to PAO inhibits PI3'-K activation, but it does not decrease either IRS-1 tyrosine-phosphorylation or the recruitment of PI3'-K to IRS-1 after insulin stimulation. PAO is also shown to inhibit PI3'-K activity in vitro. Therefore, since PI3'-K activation is essential for insulin stimulation of glucose transport, our results demonstrate that PI3'-K is a PAO-sensitive target of the insulin signaling pathway regulating glucose transport.

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:683014 HCAPLUS

DOCUMENT NUMBER: 128:1387

TITLE: Reactions of [14C]-3,4-Dichloroisocoumarin with Subunits of Pituitary and Spleen Multicatalytic Proteinase Complexes (Proteasomes)

AUTHOR(S): Orlowski, Marian; Cardozo, Christopher; Eleuteri, Anna Maria; **Kohanski, Ronald**; Kam, Chih-Min; Powers, James C.

CORPORATE SOURCE: Departments of Pharmacology Medicine and Biochemistry, Mount Sinai School of Medicine of the City University of New York, New York, NY, 10029, USA

SOURCE: Biochemistry (1997), 36(45), 13946-13953
CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Exposure to [14C]-3,4-dichloroisocoumarin (DCI) of multicatalytic proteinase complexes (MPC) isolated from bovine pituitary and spleen leads to label incorporation into several β-type subunits, to rapid inactivation of the chymotrypsin-like (ChT-L) activity, and to a slower inactivation of other activities of the MPC. The pituitary and spleen MPCs differ in that the first contains almost exclusively the X, Y, and Z subunits, whereas in the latter these subunits are largely replaced by LMP2, LMP7, and MECL1. Preincubation with two peptidyl aldehyde inhibitors of the ChT-L activity protected the X subunit in the pituitary MPC and unexpectedly the LMP2 subunit in the spleen MPC from label incorporation, despite the greater amino acid sequence homol. of the LMP7 subunit to that of the X subunit. Losses in the yield of amino acids in both subunits, shown by amino acid sequencing, and lability of the DCI-protein bond indicated formation of an acyl derivative by reaction of DCI with the threonine OH group. Brief exposure to [14C]-DCI led to preferential incorporation of label into the LMP2 and X subunits, consistent with the high inactivation rate consts. of the ChT-L activity. Z-LLF-CHO, an inhibitor of ChT-L activity, but not Z-GPFL-CHO, an inhibitor of the branched chain amino acid preferring component, prevented incorporation of radioactivity into the X subunits, whereas both inhibitors prevented label incorporation into LMP2, indicating differences in susceptibility to inhibition between the two components. These and other data are consistent with involvement of the X and LMP2 subunits in expression of the ChT-L activity in the pituitary and spleen MPC, resp., and suggest the catalytic functions of two other β-subunits.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:361900 HCAPLUS
DOCUMENT NUMBER: 127:92110
TITLE: Cis-Autophosphorylation of Juxtamembrane Tyrosines in the Insulin Receptor Kinase Domain
AUTHOR(S): Cann, Aaron Darius; **Kohanski, Ronald A.**
CORPORATE SOURCE: Department of Biochemistry, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Biochemistry (1997), 36(25), 7681-7689
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Receptor tyrosine kinases undergo ligand-induced dimerization that promotes kinase domain trans-autophosphorylation. However, the kinase domains of the insulin receptor are effectively dimerized because of the covalent α2β2 holomeric structure. This fact has made it difficult to determine the mol. mechanism of intra-holomeric autophosphorylation, but there is evidence for both cis- and trans-autophosphorylation in the absence and presence of insulin. Here, using the cytoplasmic kinase domain (CKD) of the human insulin receptor, we demonstrate that autophosphorylation in the juxtamembrane (JM) subdomain follows a cis-reaction pathway. JM autophosphorylation was independent of CKD concentration over the range 6 nM-3 μM and was characterized kinetically: half-saturation (KATP) was observed at 75 μM ATP [5 mM Mn(CH3CO2)2] with a maximal rate of 0.24 mol of PO4 (mol of CKD)-1 min-1. Pairwise substitutions of Phe for Tyr in the other two autophosphorylation subdomains, generated by site-directed mutagenesis, altered the kinetics of JM autophosphorylation but did not change the pathway from a cis-reaction. Tyr1328,1334 to Phe (in the carboxy-terminal subdomain) yielded <2-fold increase in the efficiency of JM autophosphorylation, whereas Tyr1162,1163 to Phe (in the activation loop subdomain) yielded ≈38-fold increased efficiency of JM autophosphorylation, due predominantly to a 23-fold decreased KATP. These findings demonstrate basal state binding of ATP to the CKD leading to cis-autophosphorylation and novel basal state regulatory interactions among the subdomains of the insulin receptor kinase. On the basis of these results and the crystal structure of the conserved catalytic core of this kinase [Hubbard, S. R., et al. (1994) Nature 372, 746], a model is proposed which reconciles the JM cis-reaction and the activation loop cis-inhibition/trans-reaction with the complex kinetics of insulin receptor autophosphorylation [Kohanski, R. A. (1993) Biochem. 32, 5766].
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:343063 HCAPLUS
DOCUMENT NUMBER: 127:14728
TITLE: A tyrosine kinase assay using reverse-phase high-performance liquid chromatography
AUTHOR(S): Cann, Aaron Darius; Wolf, Imre; **Kohanski, Ronald A.**
CORPORATE SOURCE: Dep. Biochem., Mount Sinai School Medicine, New York, NY, 10029, USA
SOURCE: Analytical Biochemistry (1997), 247(2), 327-332
CODEN: ANBCA2; ISSN: 0003-2697
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Reverse-phase HPLC can be used as a very precise and accurate routine

assay for peptide phosphorylation by protein kinases that has advantages over other methods. In particular, peptides with native amino acid sequences can be used without the need for radioisotopes. However, reaction conditions that are employed can often present difficulties in recovery and quantitation of phospho- and apo-peptides. Two general problems were encountered: (1) variation in the retention times of peptides and an increasing width of the injection front which can interfere with quantitation both resulted from repeated sample injections. These were caused mostly by the presence of carrier bovine serum albumin used to reduce loss of peptides during the reaction and by high concns. of ATP used to study the kinetics of enzyme catalyzed reactions. These problems were solved by regular washing of the reverse-phase column, thus allowing a broad range of peptide and ATP concns. to be used. (2) The stability of peptides used in the assay was affected by dithiothreitol in combination with Mn2+. The former is a common reagent of kinase purifications and the latter is often the metal cofactor used in kinase reactions. Minimizing the concentration of dithiothreitol or using Mg2+ resolved these difficulties. Consideration of these factors is therefore important when using reverse-phase HPLC to monitor peptide phosphorylation in protein tyrosine kinase assays.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:299945 HCAPLUS

DOCUMENT NUMBER: 127:46806

TITLE: Bovine spleen multicatalytic proteinase complex (proteasome). Replacement of X, Y, and Z subunits by LMP7, LMP2, and MECL1 and changes in properties and specificity

AUTHOR(S): Eleuteri, Anna Maria; **Kohanski, Ronald A.**; Cardozo, Christopher; Orlowski, Marian

CORPORATE SOURCE: Univ. Camerino, Camerino, 62032, Italy

SOURCE: Journal of Biological Chemistry (1997), 272(18), 11824-11831
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Amino acid sequencing of subunits of the multicatalytic proteinase complex (MPC) isolated from bovine spleen showed an almost complete replacement of the X, Y, and Z subunits, constitutively expressed in most tissues, by the interferon-γ-inducible LMP7, LMP2, and MECL1 subunits. A comparison with the pituitary MPC found a decreased chymotrypsin-like activity, a depressed peptidylglutamyl-peptide hydrolyzing activity, and a highly active component with properties similar to, but not identical with, that of the pituitary branched chain amino acid-preferring (BrAAP) component. Unlike the pituitary BrAAP component, that of the spleen MPC exhibited a greatly decreased Km, a highly increased catalytic efficiency (kcat), and a 80-180 times greater specificity constant (kcat/Km) toward substrates with either branched chain or aromatic amino acid residues in the P1 position. Also, unlike the pituitary BrAAP component, that of the spleen was sensitive to inactivation by 3,4-dichloroisocoumarin and sensitive to inhibition by peptidyl-aldehydes with either phenylalaninal or leucinal residues. Several phenylalaninal peptidyl-aldehydes were identified which selectively inhibited components of the spleen but not of the pituitary MPC. Two of the inhibitors are dipeptidyl-aldehydes, two others are tetrapeptidyl-aldehydes with a Pro residue in the P3 position. The

possibility is discussed that the properties and specificity of the spleen MPC are a consequence of the presence of the interferon-γ-inducible subunits.

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:199678 HCAPLUS
DOCUMENT NUMBER: 126:288328
TITLE: Stat5 is a physiological substrate of the insulin receptor
AUTHOR(S): Chen, Jing; Sadowski, Henry B.; **Kohanski, Ronald A.**; Wang, Lu-Hai
CORPORATE SOURCE: Department of Microbiology, Mount Sinai School of Medicine, New York, NY, 10029, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1997), 94(6), 2295-2300
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Using the cytoplasmic domain of the insulin receptor (IR) in a yeast two-hybrid screen, the authors identified a cDNA clone encoding the C-terminal 308 amino acids of human Stat5b (Stat5b-Ct). Stat5b-Ct is tyrosine phosphorylated by purified IR kinase domain in vitro. Insulin stimulates tyrosine phosphorylation of overexpressed Stat5b-Ct and endogenous Stat5 in cells overexpressing IR. Stat5 may be a direct target of the IR and, as a member of the Stat family of transcription factors, may play a role in the regulation of gene transcription by insulin. In support of this hypothesis, perfusion of mouse liver with insulin promotes rapid tyrosine phosphorylation of Stat5 and activation of Stat5 DNA binding. Moreover, refeeding of fasted mice leads to rapid tyrosine phosphorylation and stimulation of enhanced DNA-binding activity of Stat5 extracted from liver, skeletal muscle, and adipose tissues. Taken together, the authors' data strongly suggest that IR interacts with and phosphorylates Stat5 in vitro and in tissues physiol. sensitive to insulin.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 18 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:309722 HCAPLUS
DOCUMENT NUMBER: 125:3837
TITLE: Purification, identification, and properties of a Saccharomyces cerevisiae oleate-activated upstream activating sequence-binding protein that is involved in the activation of POX1
AUTHOR(S): Igor, Yi Luo; Karpichev, Igor V.; **Kohanski, Ronald A.**; Small, Gillian M.
CORPORATE SOURCE: Dep. Cell Biol./Anatomy Dep. Biochem., Mount Sinai Sch. Med., New York, NY, 10029, USA
SOURCE: Journal of Biological Chemistry (1996), 271(20), 12068-12075
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Peroxisomes have a central function in lipid metabolism, and it is well established that these organelles are inducible by many compds. including

fatty acids. Peroxisomes are the sole site for the β-oxidation of fatty acids in yeast. The first and rate-limiting enzyme of this cycle is fatty acyl-CoA oxidase. The gene encoding this enzyme in Saccharomyces cerevisiae (POX1) undergoes a complex regulation that is dependent on the growth environment. When this yeast is grown in medium containing oleic acid was the main carbon source peroxisomes are induced and POX1 expression is activated. When cells are grown in the presence of glucose, the expression of POX1 mRNA is repressed, whereas growth on a carbon source such as glycerol or raffinose causes derepression. This rigorous regulation is brought about by the complex interactions between trans-acting factors and cis-elements in the POX1 promoter. Previously the authors characterized regulatory elements in the promoter region of POX1 that are involved in the repression and activation of this gene (Wang, T., Luo, Y., and Small, G. M. (1994) J. BIol. Chemical 269, 24480-24485). In this study the authors have purified and identified an oleate-activated transcription factor (Oaflp) that binds to the activating sequence (UAS1) in the POX1 gene. The protein has a predicted mol. mass of approx. 118 kDa.

L4 ANSWER 19 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:956983 HCAPLUS
DOCUMENT NUMBER: 124:1432
TITLE: Tyrosine dephosphorylation of nuclear proteins mimics transforming growth factor β1 stimulation of α2(I) collagen gene expression
AUTHOR(S): Greenwel, Patricia; Hu, Wei; **Kohanski, Ronald A.**; Ramirez, Francesco
CORPORATE SOURCE: Brookdale Center Molecular Biology, Mt. Sinai School Medicine, New York, NY, 10029, USA
SOURCE: Molecular and Cellular Biology (1995), 15(12), 6813-19 CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Transforming growth factor β1 (TGF-β1) exerts a pos. effect on the transcription of genes coding for several extracellular matrix-related products, including collagen I. The authors have previously identified a strong TGF-β1-responsive element (TbRE) in the upstream promoter sequence of the α2(I) collagen (COL1A2) gene. The expts. have shown that TGF-β1 stimulates COL1A2 transcription by increasing binding of an Sp1-containing complex (TbRC) to the TbRE. They have also suggested that the change occurs via posttranslational modification of a protein(s) directly or indirectly interacting with Sp1. Here, the authors provide evidence showing that tyrosine dephosphorylation of nuclear proteins mimics the stimulation of COL1A2 transcription by the TGF-β1-activated signaling pathway. Preincubation of nuclear exts. with protein tyrosine phosphatase (PTPase) but not with protein phosphatase type 2A (PP2A), a serine/threonine phosphatase, enhanced binding of the TbRC to the same degree as culturing cells in TGF-β1. Consistent with these in vitro findings, genistein, a tyrosine inhibitor, led to markedly increased COL1A2 gene expression, whereas sodium orthovanadate, a tyrosine phosphatase inhibitor, decreased it substantially. These results were supported by transfection expts. showing that genistein and sodium orthovanadate have opposite effects on TbRE-mediated transcription. Moreover, nuclear proteins isolated from genistein-treated cells were found to interact with the TbRE significantly more than those from untreated cells. Furthermore, pretreatment of cells with sodium orthovanadate virtually abrogated nuclear protein binding to the TbRE, but not to a neighboring cis-acting element unresponsive to TGF-β1. The results of this study, therefore, provide the first correlation between

tyrosine dephosphorylation, increased binding of a transcriptional complex, and TGF-β1 stimulation of gene expression.

L4 ANSWER 20 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:936885 HCAPLUS
DOCUMENT NUMBER: 124:224651
TITLE: Phosphorylation of myosin regulatory light chains by the molluscan twitchin kinase
AUTHOR(S): Heierhorst, Joerg; Probst, William C.; **Kohanski, Ronald A.**; Buku, Angeliki; Weiss, Klaudiusz R.
CORPORATE SOURCE: Mount Siani School of Medicine, City University of New York, New York, NY, USA
SOURCE: European Journal of Biochemistry (1995), 233(2), 426-31
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The unusually large (≈600 to >3000 kDa) myosin-associated proteins of the titin/twitchin superfamily are considered to be important cytoskeletal rulers for thick filament assembly in muscle. This function is maintained by approx. 60-240 modular fibronectin-type-III and Ig-C2 repeats in these proteins which further contain a protein serine/threonine kinase domain of unknown function. In this study, the bacterially expressed kinase domain of Aplysia twitchin was used to identify a potential physiol. substrate. Addition of the recombinant kinase of Aplysia actomyosin prepns. resulted in the specific phosphorylation of the 19-kDa myosin regulatory light chains. The twitchin kinase phosphorylated purified light chains on Thr15 in a region which shared a high degree of similarity with the phosphorylation site for vertebrate smooth muscle myosin light chain kinase. Peptide analogs of the twitchin substrate sequence and the similar sequence in vertebrate smooth muscle myosin light chains were phosphorylated with good kinetic properties. These data reveal the first potential substrate for any of the giant protein kinases and support a dual role of twitchin in molluscan muscle as a cytoskeletal protein as well as a myosin light chain kinase.

L4 ANSWER 21 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:651898 HCAPLUS
DOCUMENT NUMBER: 123:50261
TITLE: Environments of the four tryptophans in the extracellular domain of human tissue factor: comparison of results from absorption and fluorescence difference spectra of tryptophan replacement mutants with the crystal structure of the wild-type protein
AUTHOR(S): Hasselbacher, C. A.; Rusinova, E.; Waxman, E.; Rusinova, R.; **Kohanski, R. A.**; Lam, W.; Guha, A.; Du, J.; Lin, T. C.; et al.
CORPORATE SOURCE: Departments Biochemistry, Mount Sinai School Medicine, New York, NY, 10029, USA
SOURCE: Biophysical Journal (1995), 69(1), 20-9
CODEN: BIOJAU; ISSN: 0006-3495
PUBLISHER: Biophysical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The local environments of the four tryptophan residues of the extracellular domain of human tissue factor (sTF) were assessed from difference absorption and fluorescence spectra. The difference spectra were derived by subtracting spectra from single Trp-to-Phe or Trp-to-Tyr replacement mutants from the corresponding spectrum of the wild-type

protein. Each of the mutants was capable of enhancing the proteolytic activity of factor VIIa showing that the mutations did not introduce major structural changes, although the mutants were more susceptible to denaturation by guanidinium chloride. The difference spectra indicate that the Trp residues are buried to different extents within the protein matrix. This evaluation was compared with the x-ray crystal structure of sTF. There is excellent agreement between predictions from the difference spectra and the environments of the Trp residues observed in the x-ray crystal structure, demonstrating that difference absorption and particularly fluorescence spectra derived from functional single-Trp replacement mutants can be used to obtain information about the local environments of individual Trp residues in multi-tryptophan proteins.

L4 ANSWER 22 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:258479 HCAPLUS
TITLE: Absence of insulin receptor gene mutations in three insulin-resistant women with the polycystic ovary syndrome
AUTHOR(S): Sorbara, Lynn R.; Tang, Zhichun; Cama, Alessandro; Xia, Jinru; Schenker, Esther; **Kohanski, Ronald A.**; Poretsky, Leonid; Koller, Elizabeth; Taylor, Simeon I.; Dunaif, Andrea
CORPORATE SOURCE: Coll. Med., Pennsylvania State Univ., Hershey, PA, USA
SOURCE: Metabolism, Clinical and Experimental (1994), 43(12), 1568-74
CODEN: METAAJ; ISSN: 0026-0495
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Women with polycystic ovary syndrome (PCOS) are markedly insulin-resistant, but the mol. mechanisms of these changes and their relationship to the hyperandrogenic state remain to be clarified. Mutations have recently been identified in the insulin receptor gene of patients with extreme forms of insulin resistance associated with hyperandrogenism (eg, type A insulin resistance), and these mutations account for the insulin resistance in such patients. We performed this study to determine whether mutations in the coding portion of the insulin receptor gene were responsible for insulin resistance in PCOS. Insulin binding studies using cultured skin fibroblasts of three obese (body mass index > 27 kg/m2) women with PCOS (i.e., mild hyperandrogenemia and chronic anovulation of unknown etiol.) and documented insulin resistance showed no apparent abnormalities in either the number or affinity of insulin binding sites. Direct sequencing of all 22 exons of the insulin receptor gene from two of the women with PCOS did not reveal any mutations. Furthermore, both alleles of the gene were expressed at equal levels. In a third insulin-resistant PCOS woman, there was no evidence for amutation in the coding portion of the insulin receptor gene as determined by denaturing gradient gel electrophoresis (DGGE). We conclude that the insulin resistance in these PCOS women was caused by a defect extrinsic to the insulin receptor.

L4 ANSWER 23 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:406697 HCAPLUS
DOCUMENT NUMBER: 119:6697
TITLE: A sensitive method to detect defined peptide among those eluted from murine MHC class II molecules
AUTHOR(S): Brumeanu, T. D.; **Kohanski, R.**; Bona, C. A.; Zaghouani, H.
CORPORATE SOURCE: Dep. Microbiol. and, New York, NY, 10029, USA
SOURCE: Journal of Immunological Methods (1993), 160(1), 65-71

CODEN: JIMMBG; ISSN: 0022-1759
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A sensitive competitive inhibition RIA was developed able to trace pmoles of a defined peptide eluted from major histocompatibility complex (MHC) class II mols. that were subsequently fractionated by RP-HPLC. In this assay a model synthetic peptide corresponding to amino acid residues 110-120 from the hemagglutinin (HA) of PR8 influenza virus, and affinity purified rabbit antibodies specific for this peptide were used. The HA110-120 peptide binds to I-Ed class II mols. on the surface of APCs and is recognized by specific CD4+ T helper cells. The 2PK3 B lymphoma cells (H-2d) were pulsed with HA110-120 peptide or PR8 virus, lysed, the MHC class II mols. extracted, and bound peptides eluted. After separation by RP-HPLC, the fractions were tested for inhibition of the binding of rabbit anti-HA110-120 antibodies to peptide coated microtiter plates. A significant inhibitory activity was observed with 1 peak when the cells were pulsed with HA110-120 peptide and 2 peaks when pulsed with PR8 virus. The inhibitory activity was correlated with the presence of HA110-120 peptide as demonstrated by peptide sequencing. The assay is reproducible and sensitive to 1 pmol of antigenic peptide. This assay can be useful to identify microbial peptides with defined structure and antigenicity among the multiple peptides bound to class II mols.

L4 ANSWER 24 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:401355 HCAPLUS
DOCUMENT NUMBER: 119:1355
TITLE: Insulin receptor autophosphorylation. I. Autophosphorylation kinetics of the native receptor and its cytoplasmic kinase domain
AUTHOR(S): **Kohanski, R. A.**
CORPORATE SOURCE: Dep. Biochem., Mount Sinai Sch. Med., New York, NY, 10029, USA
SOURCE: Biochemistry (1993), 32(22), 5766-72
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Kinetic anal. of autophosphorylation was done using a non-Michaelis-Menten kinetic model. This model describes autophosphorylation in terms of a fast reaction phase, a slow reaction phase, and a partition function for the two phases. Kinetic parameters determined by this new approach show that insulin stimulates autophosphorylation by promoting (1) a 10-fold increase in the rate constant for the fast phase of the reaction and (2) a 2-fold increase in the partition function favoring the fast phase. Insulin did not significantly affect the binding constant for ATP in this fast phase. Kinetic parameters obtained for the cytoplasmic kinase domain were similar to those obtained for the native insulin receptor in the absence of insulin. The insulin receptor has three subdomains encompassing its seven autophosphorylation sites. The juxtamembrane sites react primarily in the slow kinetic phase, favored by the absence of stimulation and low ATP concns. The carboxy-terminal and central autophosphorylation subdomains react primarily in the fast kinetic phase, favored by raising the ATP concentration and/or the presence of insulin. These observations demonstrate that (1) both ATP and insulin regulate reaction in each autophosphorylation subdomain, (2) insulin stimulation occurs predominantly in the central and carboxy-terminal regions, and (3) autophosphorylation observed with the cytoplasmic kinase domain was similar to native insulin receptor in the absence of insulin. These findings are consistent with conclusions based on the kinetic anal. of autophosphorylation.

L4 ANSWER 25 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:401132 HCAPLUS
DOCUMENT NUMBER: 119:1132
TITLE: Insulin receptor autophosphorylation. II. Determination of autophosphorylation sites by chemical sequence analysis and identification of the juxtamembrane sites
AUTHOR(S): **Kohanski, R. A.**
CORPORATE SOURCE: Dep. Biochem., Mount Sinai Sch. Med., New York, NY, 10029, USA
SOURCE: Biochemistry (1993), 32(22), 5773-80
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Autophosphorylation sites of the human insulin receptor were identified by microsequence anal. of 19 discrete tryptic [32P]phosphopeptides, purified from the autophosphorylated cytoplasmic kinase domain (CKD). Seventeen phosphopeptides were generated by cleavage at Arg and/or Lys, but two phosphopeptides were generated reproducibly by anomalous cleavages. Two new sites were identified in the juxtamembrane region of the intact insulin receptor β-subunit (the amino terminus of the CKD), including phosphotyrosins 965 and 972. Three sites in the central region, including phosphotyrosines 1158, 1162, and 1163, were identified from six phosphopeptides; tyrosine at 1158 was the least phosphorylated. Monophosphopeptides contained phosphotyrosine at either residue 1158 or 1163, but not at 1162. Bisphosphorylation included phosphotyrosines only at 1162 and 1163. The two autophosphorylation sites near the carboxy terminus were found in seven phosphopeptides, including phosphotyrosines at 1328 and 1334. When mapped by reverse-phase HPLC, these phosphopeptides eluted in the order central domain, first; carboxy-terminal region, second; and juxtamembrane (amino-terminal) domain, last.

L4 ANSWER 26 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:553410 HCAPLUS
DOCUMENT NUMBER: 115:153410
TITLE: The native α2β2 tetramer is the only subunit structure of the insulin receptor in intact cells and purified receptor preparations
AUTHOR(S): Schenker, Esther; **Kohanski, Ronald A.**
CORPORATE SOURCE: Dep. Biochem., Mount Sinai Sch. Med., New York, NY, 10029, USA
SOURCE: Archives of Biochemistry and Biophysics (1991), 290(1), 79-85
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The native subunit structure of the insulin receptor was reinvestigated by two-dimensional nonreducing/reducing gel electrophoresis. Human insulin receptor expressed in murine fibroblasts was a single oligomer, the α2β2 heterotetramer. The structure was assessed using receptor metabolically labeled with [35S]methionine, and using receptor autophosphorylation at two levels of purification: the insulin affinity-purified receptor and the more commonly used wheat germ agglutinin-Sepharose-enriched fraction from whole membrane exts. Lower mol. weight oligomers and free subunits were observed only upon heating the sample prior to electrophoresis. This artifact of sample handling was dependent upon three factors: (1) temperature, (2) time of heating, and (3) impurities typically present in partially purified receptor prepns. The

α2β2 tetramer is the only insulin receptor subunit structure native in intact cells and subsequently isolated from cell membranes.

L4 ANSWER 27 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:509637 HCAPLUS
DOCUMENT NUMBER: 115:109637
TITLE: Monovalent avidin affinity columns
AUTHOR(S): **Kohanski, Ronald A.**; Lane, M. Daniel
CORPORATE SOURCE: Dep. Biochem., Mt. Sinai Sch. Med., New York, NY, 10029, USA
SOURCE: Methods in Enzymology (1990), 184(Avidin-Biotin Technol.), 194-200
CODEN: MENZAU; ISSN: 0076-6879
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The preparation and characteristics of a monovalent avidin-agarose column are described. The isolation of biotin-containing compds. by affinity chromatog. using the monovalent avidin column is described.

L4 ANSWER 28 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:138793 HCAPLUS
DOCUMENT NUMBER: 114:138793
TITLE: Primary structure of avian hepatic rhodanese
AUTHOR(S): **Kohanski, Ronald A.**; Heinrikson, Robert L.
CORPORATE SOURCE: Dep. Biochem., Mount Sinai Sch. Med., New York, NY, 10029, USA
SOURCE: Journal of Protein Chemistry (1990), 9(4), 369-77
CODEN: JPCHD2; ISSN: 0277-8033
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Rhodanese (EC 2.8.1.1) (I) was purified from chicken liver and its amino acid sequence was determined I had a specificity activity of 676 IU and a mol. weight of 32,255. The primary structure of 289 amino acids was solved by sequential Edman degradation of overlapping peptides obtained by selected enzymic and chemical cleavages. The N-terminus was blocked, and the C-terminus was heterogeneous. Comparison of the primary structure with bovine liver I showed 212 identically matched amino acids, and the majority of amino acid differences were conservative substitutions. The reaction of I with a 1.4-fold molar excess of [2-14C]iodoacetate led to inactivation of the enzyme and carboxymethylation of cysteine-244; this modification was blocked by the substrate, thiosulfate.

L4 ANSWER 29 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:115422 HCAPLUS
DOCUMENT NUMBER: 114:115422
TITLE: Control of insulin receptor autophosphorylation by polypeptide substrates. Inhibition and stimulation by interaction with the catalytic subunit
AUTHOR(S): **Kohanski, R. A.**; Schenker, Esther
CORPORATE SOURCE: Dep. Biochem., Mt. Sinai Sch. Med., New York, NY, 10029, USA
SOURCE: Biochemistry (1991), 30(9), 2406-14
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Autophosphorylation of purified insulin receptor, in the absence of insulin, was stimulated by selected polypeptide substrates. In the presence of 1 μM insulin these peptides inhibited autophosphorylation. Stimulation was observed with reduced [S-(carboxamidoethyl)cysteinyl]lysozyme (RCAM-lysozyme) and three peptides generated by CNBr cleavage, V8

proteinase digestion, and/or chemical modification. Two peptide substrates were generated from RCAM-lysozyme which did not stimulate receptor autophosphorylation and were very weak inhibitors. As a control peptide, the simple substrate angiotensin inhibited receptor autophosphorylation in the absence or presence of insulin. However, stimulatory peptide, but not insulin, significantly shifted the concentration dependence for inhibition by angiotensin. The stimulatory peptides also increased autophosphorylation of the cloned cytoplasmic domain of the kinase (R-BIRK). Therefore, stimulation occurs by interaction with the cytoplasmic process of the β-subunit and not through interaction with the insulin binding α-subunit of the native receptor. Autophosphorylation was analyzed by mapping 32P-labeled tryptic phosphopeptides from the β-subunit and from R-BIRK. Nearly identical phosphopeptide maps were found, comparing first, basal R-BIRK and basal native receptor, second, peptide- and insulin-stimulated native receptor, and third, peptide-stimulated R-BIRK and insulin-stimulated native receptor. Therefore, R-BIRK functions as a basal-state enzyme and can be stimulated in an insulin-like manner. On the basis of these observations, stimulation by insulin and by peptides yields similar functional results, but by apparently different mechanisms.

L4 ANSWER 30 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:627839 HCAPLUS
DOCUMENT NUMBER: 111:227839
TITLE: Insulin receptor aggregation and autophosphorylation in the presence of cationic polyamino acids
AUTHOR(S): **Kohanski, Ronald A.**
CORPORATE SOURCE: Dep. Biochem., Mount Sinai Sch. Med., New York, NY, 10029, USA
SOURCE: Journal of Biological Chemistry (1989), 264(35), 20984-91
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Aggregation and autophosphorylation of the insulin receptor-protein kinase, from cultured 3T3-L1 adipocytes, were studied in the presence of cationic polyamino acids. Poly-L-lysine and poly-L-arginine produced the following effects with the purified receptor: first, the autophosphorylation rate was increased by polycations. Half-maximal stimulation was proportional to polymer length. The rate enhancement was greater at lower ATP concns. Second, near-endpoint (equilibrium) autophosphorylation was greater in the presence of polycations. Polycations inhibited the reverse reaction: ADP + phosphoreceptor yielding ATP + aporeceptor. Third, the [32P]phosphopeptides generated by trypsin digestion of the 32P-β-subunit, showed that no new autophosphorylation sites resulted from the presence of polycations. Fourth, the polycations, but not insulin, promoted receptor aggregation, and phosphoreceptor aggregated more readily than aporeceptor. Insulin receptor enriched through the wheat germ agglutinin eluate step was compared with purified receptor. Higher concns. of poly-L-arginine were required to stimulate autophosphorylation and to promote aggregation. Finally, several polycation-dependent substrates present in the wheat germ agglutinin eluate co-aggregated with the insulin receptor. Polycation-stimulated receptor autophosphorylation is linked to a lower KM,app for ATP, but substrate phosphorylation may require the aggregation.

L4 ANSWER 31 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1989:69710 HCAPLUS
DOCUMENT NUMBER: 110:69710
TITLE: Conformational states of the insulin receptor
AUTHOR(S): Schenker, Esther; **Kohanski, Ronald A.**

CORPORATE SOURCE: Dep. Biochem., Mt. Sinai Sch. Med., New York, NY, 10029, USA
SOURCE: Biochemical and Biophysical Research Communications (1988), 157(1), 140-5
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Insulin binding to the α-subunit of the purified insulin receptor changed the interaction between β-subunits. This conformational change was demonstrated after labeling the receptor's β-subunit by autophosphorylation in the absence of insulin, and then crosslinking the subunits to each other with bis(sulfosuccinimidyl) suberate. The covalent oligomers were resolved by reduction and denaturing gel electrophoresis. Insulin increased the rate of crosslinking, especially the formation of β-β dimers. These results support a conformational change following insulin binding, and may reflect the insulin-induced activation of autophosphorylation.

L4 ANSWER 32 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1987:490494 HCAPLUS
DOCUMENT NUMBER: 107:90494
TITLE: Effect of phenylarsine oxide on insulin-dependent protein phosphorylation and glucose transport in 3T3-L1 adipocytes
AUTHOR(S): Frost, Susan C.; **Kohanski, Ronald A.**; Lane, M. Daniel
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Journal of Biological Chemistry (1987), 262(20), 9872-6
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phenylarsine oxide (PAO) blocks insulin-stimulated glucose transport in 3T3-L1 adipocytes and the locus of inhibition is post-receptor. Insulin stimulated the extent of receptor autophosphorylation in solution and in the intact cell by .apprx.4-fold. PAO had no effect on this activity. With reduced and carboxamidomethylated lysozyme as a substrate for the tyrosine-specific receptor, insulin stimulated the rate of receptor kinase-catalyzed substrate phosphorylation by 2-fold; PAO had no effect on this stimulation. However, the insulin-stimulated, serine-specific phosphorylation of 2 endogenous phosphoproteins (pp24 and pp240) in the intact cell was blocked by 25 μM PAO. Thus, the inhibition by PAO must be distal to the insulin receptor's protein tyrosine kinase activity.

L4 ANSWER 33 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:603214 HCAPLUS
DOCUMENT NUMBER: 105:203214
TITLE: Control of autophosphorylation and substrate phosphorylation by the insulin receptor protein kinase
AUTHOR(S): Lane, M. Daniel; **Kohanski, Ronald A.**
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, USA
SOURCE: Fernstroem Foundation Series (1986), 7(Mech. Insulin Action), 59-73
CODEN: FFOSDF; ISSN: 0167-7004
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 18 refs., on the kinetics and role of autophosphorylation in substrate phosphorylation catalyzed by the insulin receptor tyrosine kinase [88201-45-0] in response to insulin [9004-10-8].

L4 ANSWER 34 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:565528 HCAPLUS
DOCUMENT NUMBER: 105:165528
TITLE: Insulin-dependent phosphorylatin of the insulin receptor-protein kinase and activation of glucose transport in 3T3-L1 adipocytes
AUTHOR(S): **Kohanski, Ronald A.**; Frost, Susan C.; Lane, M. Daniel
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Journal of Biological Chemistry (1986), 261(26), 12272-81
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Intact 3T3-L1 adipocytes were equilibrated with [32P]orthophosphate and then disrupted under denaturing conditions which preserved the phosphorylation state of the insulin [9004-10-8] receptor established in the cell. The insulin receptor, isolated by lectin adsorption and 2-dimensional nonreducing/reducing PAGE, occurred as a single oligomeric species with an apparent α2β2 subunit composition This oligomeric structure was not altered by treating cells with insulin. Only the β-subunit of the receptor was phosphorylated; [32P]phosphoserine and [32P]phosphotyrosine were both identified in the β-subunit from cells in the unstimulated state, but only [32P]phosphotyrosine increased in cells stimulated with insulin. Neither insulin-like growth factor I nor II stimulated insulin receptor β-subunit phosphorylation, although both activated hexose transport. On the addition of insulin, [32P]orthophosphate incorporated into the β-subunit increased 4.5-fold (7-fold with respect to [32P]tyrosine) and was complete within 1 min [half-time (t1/2) = 8 s]. Following the removal of insulin from the monolayers, [32P]β-subunit fell to the basal level (t1/2 = 2.5 min); there was no lag phase before either transition. The tyrosine protein kinase [80449-02-1] activity, measured in vitro with a model substrate, was higher with immunoaffinity-purified insulin receptor from insulin-stimulated cells than from cells in the basal state. Hexose transport rate, measured using 14C-labeled 3-O-methylglucose [146-72-5], was half-maximally stimulated at 2 nM insulin. A 1-min latency period followed insulin addition, after which a 7-fold increase in the steady-state rate of hexose uptake was achieved within 5 min. On the removal of insulin, hexose transport continued at the stimulated steady-state rate for 2.5 min and then declined to the basal rate with a t1/2 of 8 min. These kinetic expts. in situ and protein kinase activity measurements in vitro support the hypothesis that β-subunit phosphorylation is an intermediate step linking insulin binding to the increased glucose transport rate.

L4 ANSWER 35 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:163752 HCAPLUS
DOCUMENT NUMBER: 104:163752
TITLE: Posttranslational processing of the insulin proreceptor
AUTHOR(S): Lane, M. Daniel; Ronnett, Gabriele V.; **Kohanski, Ronald A.**; Simpson, Tracy L.
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Current Topics in Cellular Regulation (1985), 27(Modulation Covalent Modif.), 279-92
CODEN: CTCRAE; ISSN: 0070-2137

DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 28 refs., on processing of the insulin proreceptor into functional receptor in 3T3-L1 adipocytes and the importance of glycosylation in this process.

L4 ANSWER 36 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:144878 HCAPLUS
DOCUMENT NUMBER: 104:144878
TITLE: Identification and partial purification of the insulin-responsive glucose transporter from 3T3-L1 adipocytes
AUTHOR(S): Schroer, Dean W.; Frost, Susan C.; **Kohanski, Ronald A.**; Lane, M. Daniel; Lienhard, Gustav E.
CORPORATE SOURCE: Dep. Biochem., Dartmouth Med. Sch., Hanover, NH, 03756, USA
SOURCE: Biochimica et Biophysica Acta, Molecular Cell Research (1986), 885(3), 317-26
CODEN: BBAMCO; ISSN: 0167-4889
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The glucose tranporter in 3T3-L1 adipocytes has been identified as a polypeptide of average mol. weight 51,000 by its reaction with antibodies raised against the purified human erythrocyte glucose transporter and by photolabeling with [3H]cytochalasin B. The finding that the antibodies immunopptd. the photolabeled polypeptide demonstrated that both methods detected the same polypeptide. The 3T3-L1 adipocyte glucose transporter has been partially purified. The main steps in the purification procedure were the preparation of salt-washed cellular membranes, Triton X-100 solubilization, and immunoaffinity chromatog. on affinity-purified antibodies against the human erythrocyte transporter. A simple method of affinity purification of these antibodies, which consists of adsorption from serum onto protein-depleted erythrocyte membranes and release with acid, and an assay for the 3T3-L1 adipocyte transporter polypeptide which employs immunoblotting, have been developed.

L4 ANSWER 37 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:125592 HCAPLUS
DOCUMENT NUMBER: 104:125592
TITLE: Kinetic evidence for activating and non-activating components of autophosphorylation of the insulin receptor protein kinase
AUTHOR(S): **Kohanski, Ronald A.**; Lane, M. Daniel
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Biochemical and Biophysical Research Communications (1986), 134(3), 1312-18
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Reduced and carboxamidomethylated-lysozyme (RCAM-lysozyme) is an excellent substrate (Km = 13 μM) and a potent inhibitor of insulin receptor protein kinase autophosphorylation (Ki = 0.6 μM). By using these properties of RCAM-lysozyme, autophosphorylation was resolved into 2 kinetically and functionally distinct components involving formation of phosphotyrosine on the receptor β-subunits. Insulin-stimulated autophosphorylation is independent of autophosphorylation at other sites; activation of insulin receptor-catalyzed substrate phosphorylation is dependent upon this component of autophosphorylation, which is inhibited

by RCAM-lysozyme. Autophosphorylation at saturating RCAM-lysozyme concentration is
insensitive to insulin and has little effect on substrate phosphorylation. Thus, only insulin-dependent receptor autophosphorylation is responsible for activation of kinase-catalyzed substrate phosphorylation.

L4 ANSWER 38 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:123217 HCAPLUS
DOCUMENT NUMBER: 104:123217
TITLE: Post-translational processing and activation of insulin and EGF proreceptors
AUTHOR(S): Lane, M. Daniel; Ronnett, Gabriele; Slieker, Lawrence J.; **Kohanski, Ronald A.**; Olson, Tracy L.
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Biochimie (1985), 67(10-11), 1069-80
CODEN: BICMBE; ISSN: 0300-9084
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 35 refs., on the role of glycosylation on the post-translational processing of the insulin [9004-10-8] and EGF [62229-50-9] proreceptor polypeptides.

L4 ANSWER 39 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1985:589938 HCAPLUS
DOCUMENT NUMBER: 103:189938
TITLE: Synthesis and processing of the insulin proreceptor to form functional insulin receptor
AUTHOR(S): Lane, M. Daniel; Ronnett, Gabriele V.; **Kohanski, Ronald A.**; Simpson, Tracy L.
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: UCLA Symposia on Molecular and Cellular Biology, New Series (1985), 23(Membr. Recept. Cell. Regul.), 397-412
CODEN: USMBD6; ISSN: 0735-9543
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 26 refs., on the importance of glycosylation in the processing of the insulin [9004-10-8] proreceptor to form functional insulin receptor. Purification of the insulin receptor, posttranslational activation of the proreceptor, and identification of the intermediates in the processing pathway are discussed.

L4 ANSWER 40 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1985:556541 HCAPLUS
DOCUMENT NUMBER: 103:156541
TITLE: Receptor affinity chromatography
AUTHOR(S): **Kohanski, Ronald A.**; Lane, M. Daniel
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Annals of the New York Academy of Sciences (1985), 447(Biotin), 373-85
CODEN: ANYAA9; ISSN: 0077-8923
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 27 refs. on the chromatog. isolation of the insulin receptor using a bifunctional biotin-hormone conjugate and immobilized avidin to retain the complex between receptor and the bifunctional ligands.

L4 ANSWER 41 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1985:419252 HCAPLUS
DOCUMENT NUMBER: 103:19252
TITLE: Homogeneous functional insulin receptor from 3T3-L1 adipocytes. Purification using NαB1-(biotinyl-ε-aminocaproyl)insulin and avidin-Sepharose
AUTHOR(S): **Kohanski, Ronald A.**; Lane, M. Daniel
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Journal of Biological Chemistry (1985), 260(8), 5014-25
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Insulin receptor was purified 10,000-fold from cultured mouse 3T3-L1 adipocytes in 35% overall yield. The specific activities of 125I-labeled insulin binding and autophosphorylation increased in parallel, following the initial Triton X 100 extraction of membranes. The isolation protocol, performed entirely at pH 8.45, entailed adsorption by avidin-Sepharose CL 4B of a complex formed between Triton X 100-solubilized insulin receptor and NαB1-(biotinyl-ε-aminocaproyl)insulin, and the specific elution of the complex with biotin. The avidin-Sepharose CL 4B was a partially denatured preparation, showing estimated dissociation consts. of 0.2 μM for biotin and .apprx.1 μM for the bifunctional ligand at pH 7, 4°. The bifunctional ligand was characterized by 70% competency in binding to avidin, 100% competency in binding to solubilized insulin receptor, full stimulation of autophosphorylation of the isolated receptor, and maximal stimulation of hexose uptake by intact 3T3-L1 adipocytes. The insulin-binding properties of the insulin receptor were uniform throughout this purification procedure. At pH 8.45, 4°, an average Kd = 0.72 nM was determined for a single class of noninteracting insulin-binding sites. The apparent autophosphorylation of the β-subunit was also unchanged following affinity chromatog. A single oligomeric structure was established for the purified receptor, composed only of 135,000- and 95,000-dalton subunits whose association was lost by denaturation in the presence of reducing agent. This single structure occurred in the initial Triton X 100 extract The purified insulin receptor was capable of autophosphorylating the β-subunit and catalyzed phosphorylation of protein substrates.

L4 ANSWER 42 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1984:168791 HCAPLUS
DOCUMENT NUMBER: 100:168791
TITLE: Role of glycosylation in the processing of newly translated insulin proreceptor in 3T3-L1 adipocytes
AUTHOR(S): Ronnett, Gabriele V.; Knutson, Victoria P.; **Kohanski, Ronald A.**; Simpson, Tracy L.; Lane, M. Daniel
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Journal of Biological Chemistry (1984), 259(7), 4566-75
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A procedure was developed for the immunopptn. of glycosylated and nonglycosylated forms of the insulin [9004-10-8] receptor and its precursors without prior purification using lectins. 3T3-L1 adipocytes were labeled with [35S]methionine after which 35S-labeled receptor polypeptides

were specifically immunopptd. and characterized by SDS-polyacrylamide gel electrophoresis. The 1st 35S-polypeptide detected was a 190-kilodalton (kDa) glycosylated proreceptor which was rapidly [half-time (t1/2) .simeq. 15 min] processed to a 210-kDa intermediate. The latter precursor was more slowly (t1/2 .simeq. 2 h) proteolytically processed to 125-kDa (α') and 83-kDa (β') precursors of the mature α- and β-receptor subunits. Immediately prior to insertion into the plasma membrane, i.e. .apprx.3 h after translation, the α'- and β'-precursor polypeptides were converted to the mature 135-kDa α- and 95-kDa β-receptor subunits. The characteristics of the oligosaccharide moieties of the receptor precursors and products were investigated. The 210-kDa precursor and its 2 products, the 125-kDa α'- and 83-kDa β'-species, and the mature α- and β-receptor subunits bound tightly to wheat germ lectin, whereas the 190-kDa proreceptor species did not. On incubation with endoglycosidase H, both the 210- and 190-kDa species were converted to a 180-kDa species. The 125-kDa α'- and 83-kDa β'-species were also cleaved by endoglycosidase H, being reduced in size to 97 and 79 kDa, resp. Based on their sensitivity to endoglycosidase H and insensitivity to neuraminidase, the oligosaccharide chains of the receptor precursors (190, 210, 125, and 83 kDa) did not contain terminal sialic acid (or other capping sugars). However, near the time of insertion into the plasma membrane, capping of the α'- and β'-species by sialic acid occurred, giving rise to the mature 135-kDa α- and 95-kDa β-receptor subunits, which were partially endoglycosidase H-resistant and neuraminidase-sensitive. When 3T3-L1 adipocytes were treated with tunicamycin, a 180-kDa proreceptor aglycopolypeptide was synthesized which was incapable of undergoing further processing and proteolytic cleavage to the α- and β (or α'- and β'-)-subunits. The 180-kDa species, which appeared to be the aglyco-form of the 190-kDa proreceptor generated by endoglycosidase H, was resistant to trypsin in the intact cell and apparently had not reached the cell surface. Thus, the oligosaccharide moieties of the insulin receptor precursor are crucial for proper processing, intracellular translocation, and formation of functionally competent insulin receptor.

L4 ANSWER 43 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1983:433469 HCAPLUS
DOCUMENT NUMBER: 99:33469
TITLE: Binding of insulin to solubilized insulin receptor from human placenta. Evidence for a single class of noninteracting binding sites
AUTHOR(S): **Kohanski, Ronald A.**; Lane, M. Daniel
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Journal of Biological Chemistry (1983), 258(12), 7460-8
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Binding of 125I-labeled insulin [9004-10-8] to insulin receptor was studied at equilibrium using plasma membrane protein, from human placenta, solubilized in Triton X-100. Measured at 1 nM [125I]insulin, the amount of radioligand bound specifically was dependent on pH, with the optimal association at 4° occurring in the pH range 8.2-8.7. The Adair equation was employed for anal. of binding isotherms generated at several pH values for concns. of radioligand of 0.01-8.0 nM. Association consts. derived from these analyses showed the same pH dependence described above and were independent of receptor concentration Hill plots derived from these titrns. consistently yielded Hill coeffs. of 1 and Scatchard plots gave

virtually straight lines. Close correspondence was found between theor. analyses and observations under all exptl. conditions and graphical methods employed. These results are consistent with a single class of noninteracting [125I]insulin binding sites on the solubilized insulin receptor.

L4 ANSWER 44 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1982:435084 HCAPLUS
DOCUMENT NUMBER: 97:35084
TITLE: Rhodanese: structure-function relationships relevant to the mechanisms of cyanide detoxication
AUTHOR(S): Keim, Philip; **Kohanski, Ronald A.**; Heinrikson, Robert L.
CORPORATE SOURCE: Dep. Biochem., Univ. Chicago, Chicago, IL, 60637, USA
SOURCE: Antinutr. Nat. Toxicants Foods, [Pap. Symp.] (1981), Meeting Date 1979, 331-58. Editor(s): Ory, Robert L. Food & Nutr. Press: Westport, Conn.
CODEN: 47ZOAW
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review with 61 refs.

L4 ANSWER 45 OF 45 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1977:479143 HCAPLUS
DOCUMENT NUMBER: 87:79143
TITLE: A simple quantitative assay of iodine-125-labeled α-bungarotoxin binding to soluble and membrane-bound acetylcholine receptor protein
AUTHOR(S): **Kohanski, Ronald A.**; Andrews, John P.; Wins, Pierre; Eldefrawi, Mohyee E.; Hess, George P.
CORPORATE SOURCE: Sect. Biochem. Mol. Biol., Cornell Univ., Ithaca, NY, USA
SOURCE: Analytical Biochemistry (1977), 80(2), 531-9
CODEN: ANBCA2; ISSN: 0003-2697
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This method involves the irreversible formation of a complex between 125I-labeled α-bungarotoxin [11032-79-4], and the acetylcholine [51-84-3], receptor in either its membrane-bound or purified state. The separation of the labeled toxin-receptor complex from unreacted toxin is accomplished by chromatog. on carboxmethylcellulose cation-exchange resin. The method described was developed to satisfy the following exptl. requirements that could not be dealt with in their entirety by employing any of the published methods: (i) the complete recovery of reacted and unreacted species in relatively small volumes; (ii) an efficient and precise isolation of the specific and irreversible 125I-labeled α-bungarotoxin-receptor complex when the complexation reactions demand a large excess of unlabeled α-bungarotoxin for quenching (a 20-fold molar excess of unlabeled over labeled toxin); (iii) this isolation of the toxin-receptor complex allows one to determine the protein concns. in the samples, a necessity in expts. covering a wide range of receptor concns.; (iv) a consistent low blank for binding site concns. ranging over two or three orders of magnitude; and (v) simplicity and rapidity.

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L2 57 SEA FILE=HCAPLUS ABB=ON PLU=ON ("PARANG K"/AU OR "PARANG KAYKAVOOS"/AU OR "PARANG KEYKAVOUS"/AU)
L3 8 SEA FILE=HCAPLUS ABB=ON PLU=ON ("ABLOOGLU ARARAT J"/AU OR

"ABLOOGLU ARARAT JAN"/AU OR "ABLOOGU ARARAT"/AU) NOT L2
L4 45 SEA FILE=HCAPLUS ABB=ON PLU=ON ("KOHANSKI R"/AU OR "KOHANSKI R A"/AU OR "KOHANSKI RON"/AU OR "KOHANSKI RON A"/AU OR "KOHANSKI RONALD"/AU OR "KOHANSKI RONALD A"/AU) NOT (L2 OR L3)
L5 22 SEA FILE=HCAPLUS ABB=ON PLU=ON ("COURTNEY A"/AU OR "COURTNEY A D"/AU OR ("COURTNEY ALIYA"/AU OR "COURTNEY ALIYA D"/AU)) NOT (L2 OR L3 OR L4)

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L5 ANSWER 1 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:1035398 HCAPLUS
TITLE: Requisite role for complement C5 and the C5a receptor in granulomatous response to mycobacterial glycolipid trehalose 6,6'-dimycolate
AUTHOR(S): Borders, C. W.; **Courtney, A.**; Ronen, K.; Laborde-Lahoz, M. Pilar; Guidry, T. V.; Hwang, S.-A.; Olsen, M.; Hunter, R. L., Jr.; Hollmann, T. J.; Wetsel, R. A.; Actor, J. K.
CORPORATE SOURCE: Medical School, University of Texas-Houston, Houston, TX, USA
SOURCE: Scandinavian Journal of Immunology (2005), 62(2), 123-130
CODEN: SJIMAX; ISSN: 0300-9475
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The development of pulmonary granulomatous lesions during mycobacterial infection is a complex phenomenon, in part caused by responses elicited towards the surface glycolipid trehalose 6,6'-dimycolate (TDM; cord factor). The mol. mechanisms underlying granuloma formation following challenge with TDM are not yet completely understood. The present study defines pathol. differences in acute response to Mycobacterium tuberculosis TDM in C57BL/6 mice and mice lacking the C5a receptor (C5aR-/-). Mice were i.v. injected with TDM prepared in water-in-oil-in-water emulsion and examined for histol. response and changes in proinflammatory cytokines and chemokines in lung tissue. Control C5a receptor-sufficient mice demonstrated a granulomatous response that peaked between days 4 and 7. Increased production of macrophage inflammatory protein-1 alpha (MIP-1α), interleukin-1β (IL-1β) and CXC chemokine KC (CXCL1) correlated with development of granulomas, along with modest change in tumor necrosis factor-alpha (TNF-α). In contrast, the C5aR-/- mice revealed markedly exacerbated inflammatory response. The receptor-deficient mice also demonstrated a lack of coherent granulomatous response, with severe edema present and instances of lymphocytic cuffing around pulmonary vessels. Lung weight index was increased in the C5aR-/- mice, correlating with increased MIP-1α, KC, IL-1β and TNF-α over that identified in the congenic C5aR-sufficient controls. Correlate expts. performed in C5-deficient (B10.D2-H2d H2-T18c Hco/oSnJ) mice revealed similar results, leading to the conclusion that C5 plays a significant role in mediation of chemotactic and activation events that are the basis for maturation of granulomatous responses to TDM.
REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:266327 HCAPLUS

DOCUMENT NUMBER: 138:380914
TITLE: Chemical Approaches to Reversible Protein Phosphorylation
AUTHOR(S): Cole, Philip A.; **Courtney, Aliya D.**; Shen, Kui; Zhang, Zhongsen; Qiao, Yingfeng; Lu, Wei; Williams, Daniel M.
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Accounts of Chemical Research (2003), 36(6), 444-452
CODEN: ACHRE4; ISSN: 0001-4842
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Protein phosphorylation catalyzed by protein kinases plays a critical role in cellular signaling. Here we review several chemical approaches to understanding protein kinases and the consequences of protein phosphorylation. We discuss the design of bisubstrate analog inhibitors based on a dissociative transition state, the development of reagents for crosslinking protein kinases with their substrates, the chemical rescue of mutant protein tyrosine kinases, and the application of expressed protein ligation to understanding protein phosphorylation.
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:851034 HCAPLUS
DOCUMENT NUMBER: 138:45018
TITLE: Deformation and bonding in a puckered Re-C square net
AUTHOR(S): Merschrod S., Erika F.; **Courtney, Aliya**; Hoffmann, Roald
CORPORATE SOURCE: Dep. Chemistry CHemical Biology, Cornell Center Materials Res., Cornell Univ., Ithaca, NY, 14853-1301, USA
SOURCE: Zeitschrift fuer Anorganische und Allgemeine Chemie (2002), 628(12), 2757-2763
CODEN: ZAACAB; ISSN: 0044-2313
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Sc5Re2C7 contains unusual Re-C puckered "square" nets, isolated C3 units, and scandium ions. Its electron count drives the peculiar distortion of the Re-C nets, resulting in quite different Re-C and Re-Re bonding along each direction. Indeed, some of the Re-C interactions emerge as stronger than double bonds. The puckering, in turn, enables a bonding role for the scandium atoms in addition to their function as electron donors to the nets and the isolated carbide units.
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:515071 HCAPLUS
DOCUMENT NUMBER: 133:248858
TITLE: p300/CBP-associated factor histone acetyltransferase processing of a peptide substrate. Kinetic analysis of the catalytic mechanism
AUTHOR(S): Lau, Ontario D.; **Courtney, Aliya D.**; Vassilev, Alex; Marzilli, Lisa A.; Cotter, Robert J.; Nakatani, Yoshihiro; Cole, Philip A.

CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Journal of Biological Chemistry (2000), 275(29), 21953-21959
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB P300/CBP-associated factor (PCAF) is a histone acetyltransferase that plays an important role in the remodeling of chromatin and the regulation of gene expression. It has been shown to catalyze preferentially acetylation of the ε-amino group of lysine 14 in histone H3. In this study, the kinetic mechanism of PCAF was evaluated with a 20-amino acid peptide substrate derived from the amino terminus of histone H3 (H3-20) and recombinant bacterially expressed PCAF catalytic domain (PCAFcat). The enzymol. behavior of full-length PCAF and PCAFcat were shown to be similar. PCAF-catalyzed acetylation of the substrate H3-20 was shown to be specific for Lys-14, analogous to its behavior with the full-length histone H3 protein. Two-substrate kinetic anal. displayed an intersecting line pattern, consistent with a ternary complex mechanism for PCAF. The dead-end inhibitor analog desulfo-CoA was competitive vs. acetyl-CoA and noncompetitive vs. H3-20. The dead-end analog inhibitor H3-20 K14A was competitive vs. H3-20 and uncompetitive vs. acetyl-CoA. The potent bisubstrate analog inhibitor H3-CoA-20 was competitive vs. acetyl-CoA and noncompetitive vs. H3-20. Taken together, these inhibition patterns support an ordered BiBi kinetic mechanism for PCAF in which acetyl-CoA binding precedes H3-20 binding. Viscosity expts. suggest that diffusional release of product is not rate-determining for PCAF catalysis. These results provide a mechanistic framework for understanding the detailed catalytic behavior of an important subset of the histone acetyltransferases and have significant implications for mol. regulation of and inhibitor design for these enzymes.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1996:267237 HCAPLUS
DOCUMENT NUMBER: 124:310185
TITLE: An assessment of the possible reasons for differential tolerance to fluroxypyr in selected populations of Galium aparine
AUTHOR(S): Hill, A. L.; **Courtney, A. D.**; Harvey, B. M. R.
CORPORATE SOURCE: Agriculture and Food Science Centre, Queen's University, Belfast, BT9 5PX, UK
SOURCE: Weed Research (1996), 36(1), 15-20
CODEN: WEREAT; ISSN: 0043-1737
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In an investigation of the possible reasons for tolerance to fluroxypyr by G. aparine, a wide range of variation in total herbicide retention was exhibited by 9 diverse populations from throughout Europe. Although these differences in fluroxypyr retention became negligible when considered on a unit area basis, a two-fold difference was maintained per unit dry matter. There was no difference in fluroxypyr uptake between a fluroxypyr-tolerant and a fluroxypyr-susceptible population, and differences in translocation between the two populations did not seem to explain the differential

tolerance. Differential metabolic detoxification may be the main reason for the variation in response to fluroxypyr by populations of G. aparine.

L5 ANSWER 6 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:501849 HCAPLUS
DOCUMENT NUMBER: 121:101849
TITLE: The significance of crop density on the tolerance of irrigated crops to pendimethalin in the Sudan
AUTHOR(S): Tom, S. El; **Courtney, A. D.**
CORPORATE SOURCE: Dep. Appl. Plant Sci., Queen's Univ. Belfast, BT9 5PX, UK
SOURCE: Brighton Crop Protection Conference--Weeds (1993), (VOL. 2), 647-8
CODEN: BCPWE2; ISSN: 0955-1514
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of crop d. on crop tolerance to pendimethalin was tested in two field trials in the Sudan. Each of the crops sorghum, oats and pigeon pea showed increased mortality during establishment with increasing d. The effects were most significant in sorghum, the most sensitive crop to pendimethalin. This response is contrary to the more often recorded effect of d. where crop tolerance is increased by higher crop stands.

L5 ANSWER 7 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:250369 HCAPLUS
DOCUMENT NUMBER: 116:250369
TITLE: Cost-effectiveness of weed control in cereals - systems based on thresholds and reduced rates
AUTHOR(S): Proven, M. J.; **Courtney, A.**; Picton, J.; Davies, D. H. K.; Whiting, A. J.
CORPORATE SOURCE: Agric. Dev. Advis. Serv., Drayton Exp. Husb. Farm., Stratford upon Avon/Warwickshire, CV37 9RQ, UK
SOURCE: Brighton Crop Protection Conference--Weeds (1991), (Vol. 3), 1201-8
CODEN: BCPWE2; ISSN: 0955-1514
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A series of trials was established in farm cereal crops on 10 sites throughout the United Kingdom in the 1987/88 season. The experiment was designed to test in practice systems of weed control which placed differing degrees of reliance on weed threshold models developed at Long Ashton Research Station. It also studied the effectiveness of systems which reduced herbicide inpt by halving the product applicaltion rates. Weed populations were monitored, both to determine the need for treatment in threshold-managed systems and, by comparison with untreated areas, to assess herbicide efficacy. Over a wide range of soil types and locations, on typical arable farms, the risk-aversive thresholds were exceeded on about 80% of occasions. The reduction in efficacy when herbicide rate was reduced by 50% from that recommended on the product label was, over a wide range of situations, small. Grain yield was generally unaffected by frequency of herbicide use or by herbicide rate. As a direct consequence, the most cost-effective strategies were those which involved the least expenditure on herbicides.

L5 ANSWER 8 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:250357 HCAPLUS
DOCUMENT NUMBER: 116:250357
TITLE: The relative influence of genetic variation and provenance on the morphology and herbicide response of selected populations of Galium aparine

AUTHOR(S): Hill, A. L.; **Courtney, A. D.**
CORPORATE SOURCE: Agric. Bot. Dep., Queens Univ. Belfast, Belfast, BT9 5PX, UK
SOURCE: Brighton Crop Protection Conference--Weeds (1991), (Vol. 3), 1015-22
CODEN: BCPWE2; ISSN: 0955-1514
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Seeds of Galium aparine, collected from locations in 5 European countries, were grown in Germany and Northern Ireland. Plants grown from seed from these sites were then compared along with plants from the original seed collection. A significant effect of provenance, population and an interaction between the 2 were found with respect to seed size, percentage germination, and some seedling characters. Significant population differences in response to fluroxypyr were unaffected by the provenance of the seeds.

L5 ANSWER 9 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:419342 HCAPLUS
DOCUMENT NUMBER: 113:19342
TITLE: The effect of crop density on herbicide efficacy and yield response in continuous spring barley
AUTHOR(S): Easson, D. L.; **Courtney, A. D.**
CORPORATE SOURCE: Agric. Res. Inst. North. Ireland, Hillsborough, BT26 6DR, UK
SOURCE: Brighton Crop Protection Conference--Weeds (1989), (1), 137-42
CODEN: BCPWE2; ISSN: 0955-1514
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A spring barley experiment was carried out in which herbicide (Advance; Twin-Tak; Seritox 50; Ally) and crop d. treatments were imposed on two cultivars on the same plots for four years. In the absence of herbicide broad-leaved weed nos. progressively increased from 106 m-2 to 194 m-2 over the four years. This contrasts with the Poa annua population, which exhibited a general decline on all treatments. The herbicide treatments reduced broad-leaved weed nos. and progressively increased yields. Reducing the crop d. influenced weed biomass rather than weed nos. with the highest response to herbicides occurring at the lowest crop d. The herbicide treatments showed significantly different yield responses which appear to be attributable to factors other than weed control efficacy.

L5 ANSWER 10 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1988:506460 HCAPLUS
DOCUMENT NUMBER: 109:106460
TITLE: A comparison of herbicides for weed control in fiber flax
AUTHOR(S): **Courtney, A. D.**
CORPORATE SOURCE: Agric. Bot. Res. Div., Dep. Agric. N. Ireland, Belfast, BT9 5PX, UK
SOURCE: Annals of Applied Biology (1988), 112(Suppl.), 50-1
CODEN: AABIAV; ISSN: 0003-4746
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Of 6 preemergence herbicides, Butisan S 500, aclonifen 3000, and Tristar 1104 kg/ha, were the most effective, controlling weeds and increasing the yield of fiber flax by 38, 34, and 32%, resp. Postemergence Ally 3 g/ha or Vulcan (bromoxynil 240 + clopyralid 50 g/ha) increased the yield by 29 and 28%, resp.

L5 ANSWER 11 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1987:631307 HCAPLUS
DOCUMENT NUMBER: 107:231307
TITLE: Weed incidence and yield response to herbicides in spring barley (Hordeum vulgare) on farm sites in Northern Ireland
AUTHOR(S): **Courtney, A. D.**; Johnston, R. T.
CORPORATE SOURCE: Agric. Bot. Res. Div., Dep. Agric. North. Ireland, Belfast, BT9 5PX, UK
SOURCE: Record of Agricultural Research (1987), 35, 11-15
CODEN: RARIAQ; ISSN: 0375-0698
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In an investigation conducted at 41 farm sites between 1978 and 1981, no significant yield response was recorded to application of herbicides (MCPA, MCPA-dichlorprop mixture, ioxynil-bromoxynil-mecoprop mixture) to spring barley, but a regression anal. indicated a significant reduction in yield due to an increase in the number of weeds. The average weed population was 184 weeds/m2. The most frequent species was Stellaria media followed by Polygonum persicaria and annual grass weeds.

L5 ANSWER 12 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1987:511005 HCAPLUS
DOCUMENT NUMBER: 107:111005
TITLE: A comparison of herbicide regimes for weed control in fiber flax
AUTHOR(S): **Courtney, A. D.**
CORPORATE SOURCE: Agric. Bot. Res. Div., Dep. Agric. N. Ireland, Belfast, BT9 5PX, UK
SOURCE: Tests of Agrochemicals and Cultivars (1987), 8, 84-5
CODEN: TACUDC; ISSN: 0951-4309
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The standard unincorporated trifluralin treatment failed to give adequate control of either dicotyledonous or grass weeds. Metazachlor was the best treatment against grass weeds but some initial effects on crop establishment were observed, suggesting that crop tolerance may not be sufficient. Each of the sulfonyl urea treatments even at the lowest rates produced excellent control of the main weed species present at the two sites, Polygonum persicaria, Galeopsis tetrahit, Spergula arvensis, Ranunculus repens, and Chamomilla suaveolens. The bromoxynil + clopyralid treatment caused distortion of the crop and, with bentazon, gave inadequate weed control. Effects on crop yield were not statistically significant.

L5 ANSWER 13 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1987:80241 HCAPLUS
DOCUMENT NUMBER: 106:80241
TITLE: A comparison of herbicide regimes for weed control in fiber flax
AUTHOR(S): **Courtney, A. D.**
CORPORATE SOURCE: Agric. Bot. Res. Div., Dep. Agric. North. Ireland, Belfast, BT9 5PX, UK
SOURCE: Tests of Agrochemicals and Cultivars (1986), 7, 88-9
CODEN: TACUDC; ISSN: 0951-4309
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Preemergence treatments only gave consistent weed control in flax when used in sequence with Pardner (bromoxynil) or Vulcan (bromoxynil-

clopyralid mixture). Early postemergence application of Finesse (metsulfuron-chlorsulfuron mixture) [76363-65-0] also gave good control. Control of Polygonum aviculare was improved by the use in sequence of Pardner. At 960 g/ha, Chandor [8070-92-6] caused basal callus formation and fracture of some stems. At 20 g/ha, Finesse caused severe crop stunting. Both Pardner and Vulcan caused some temporary distortion in crop growth.

L5 ANSWER 14 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1986:124975 HCAPLUS
DOCUMENT NUMBER: 104:124975
TITLE: Pre-harvest retting of flax: uptake, translocation and efficacy of glyphosate applied to flax in a dry year
AUTHOR(S): Harvey, B. M. R.; Crothers, S. H.; **Courtney, A. D.**
CORPORATE SOURCE: Agric. Bot. Res. Div., Dep. Agric. North. Ireland, Belfast, BT9 5PX, UK
SOURCE: Record of Agricultural Research (1985), 33, 87-93
CODEN: RARIAQ; ISSN: 0375-0698
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The uptake, translocation, and efficacy of glyphosate [1071-83-6] in promoting the preharvest retting of flax were studied in the abnormally dry summer of 1984. Cultivar Hera was sprayed with glyphosate (1.44 kg/ha) 12 days after the mid-point of flowering, when the soil moisture deficit (SMD) was 114 mm. 14C-labeled glyphosate was applied to the upper leaves of the main stem immediately after spraying and the distribution of 14C was determined at 20, 48 and 120 h after treatment. More than 90% had been taken ≤48 h after application, and by 120 h 86% of the applied glyphosate had been translocated out of the treated leaves. Most of the translocated glyphosate (66%) accumulated in the capsules. Cultivars Ariane, Natasja, and Regina were sprayed at 13, 12, and 15 days, resp., after the mid-point of flowering (SMD 117 mm). No varietal differences in uptake or translocation of 14C-glyphosate were found. Rainfall reduced the SMD to 86 mm at the end of the second week after spraying and by the 4th week all varieties had desiccated to <18% moisture content. Thus, the slow desiccation of Hera was not due to poor uptake of glyphosate or to poor translocation out of the treated leaves. The absorbed glyphosate remained potentially active and caused desiccation when rainfall was sufficient to relieve plant moisture stress.

L5 ANSWER 15 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1983:84803 HCAPLUS
DOCUMENT NUMBER: 98:84803
TITLE: Preharvest retting of flax: a light microscope study of the effects of glyphosate treatment on the maturation of stem tissues
AUTHOR(S): Fraser, T. W.; **Courtney, A. D.**; Harvey, B. M. R.
CORPORATE SOURCE: Plant Pathol. Res. Div., Dep. Agric. Northern Ireland, Belfast, BT9 5PX, UK
SOURCE: Annals of Applied Biology (1982), 101(3), 533-7
CODEN: AABIAV; ISSN: 0003-4746
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A range of glyphosate [1071-83-6] treatments was applied to flax at 3 stages of flowering. Spraying at a rate equivalent to 1.4 kg/ha at the start of flowering gave satisfactorily uniform premature desiccation and was selected for a light-microscopic investigation of the effects of the

herbicide on stem tissues. During normal maturation, increase in fiber cell wall thickness, lignification of the fibers, and differentiation of the secondary xylem continued for 3-5 wk after the beginning of flowering. This differentiation was halted by the application of glyphosate. Three wk after treatment various types of tissue damage were observed In some sections epidermal and cortical cells showed the most damage, this being consistent with herbicide uptake at the stem surface. In other sections phloem and associated parenchyma cells showed the most damage. Disintegration of phloem and cortical cells occurred in some treated stem segments and caused separation of the fiber bundles from surrounding tissues. This resembled the release of fiber bundles which results from conventional postharvest retting. The potential of glyphosate application to flax as a preharvest retting technique is discussed.

L5 ANSWER 16 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1982:594511 HCAPLUS
DOCUMENT NUMBER: 97:194511
TITLE: An evaluation of the selective herbicidal activity of soil sterilants based on methyl isothiocyanate
AUTHOR(S): Wilson, Ruth E.; **Courtney, A. D.**
CORPORATE SOURCE: Dep. Agric. Bot., Queen's Univ. Belfast, Belfast, BT9 5PX, UK
SOURCE: Theory Pract. Use Soil Appl. Herbic., Symp. (1981), 291-8. Eur. Weed Res. Soc.: Paris, Fr.
CODEN: 48SBAX
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Soil samples were stored at 278 K for 4 wk to induce cold stratification of weed seed, treated with Dazomet (I) [533-74-4] at 10, 20, or 40 g/m2, and placed on seed trays. I decreased seedling emergence to 63, 41, and 23% of controls resp. Emergence in nonstratified samples was decreased to 53, 76, and 14% of controls, resp. which shows that 20 g I/m2 stimulated germination of non-stratified weed seed. In seed soaking treatments, using metham-sodium [137-42-8], a wide variation in species tolerance was observed Broad-leaved dock (Rumex obtusifolius) was very tolerant, while barley (Hordeum vulgare), perennial ryegrass (Lolium perenne), wild oat (Avena fatua), and rough-stalked meadow grass (Poa trivialis) were very susceptible. Sublethal concns. of metham-Na stimulated germination, especially in Lepidium sativum. Thus, both methyl isothiocyanate [556-61-6] generators affected germination in analogous ways, consisting of concomitant inhibition and stimulation which may involve breakdown products.

L5 ANSWER 17 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1981:582194 HCAPLUS
DOCUMENT NUMBER: 95:182194
TITLE: Evaluation of DPX 4189 for selective weed control in grassland
AUTHOR(S): McAteer, S.; **Courtney, A. D.**
CORPORATE SOURCE: Dep. Agric. Bot., Queen's Univ., Belfast, UK
SOURCE: Tests of Agrochemicals and Cultivars (1981), 2, 48-9
CODEN: TACUDC; ISSN: 0951-4309
DOCUMENT TYPE: Journal
LANGUAGE: English
AB DPX 4189 [64902-72-3] (20 or 40 g/ha) decreased the dry matter yield of Lolium perenne, L. multiflorum, Festuca pratensis, and F. prundinacea. Dactylis glomerata Was only moderately sensitive to DPX 4189.

L5 ANSWER 18 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1981:436995 HCAPLUS

DOCUMENT NUMBER: 95:36995
TITLE: The effect of herbicides on the dry matter yield and regrowth elongation of an established Lolium perenne (ryegrass) sward
AUTHOR(S): **Courtney, A. D.**; Johnson, R. M.
CORPORATE SOURCE: Field Bot. Res. Div., Dep. Agric. North. Ireland, Belfast, BT9 5PX, UK
SOURCE: Proceedings - British Crop Protection Conference--Weeds (1980), 15(2), 589-94
CODEN: PBCWDF; ISSN: 0144-1604
DOCUMENT TYPE: Journal
LANGUAGE: English
AB When applied at recommended rates,the herbicides asulam [3337-71-1], mecoprop [7085-19-0] and dicamba [1918-00-9] with mecoprop produced no significant effects on annual dry matter (d.m.) yields of perennial ryegrass; even in seasons when the swards were subject to considerable drought stress, severe depressions of yield occurred at some individual harvests. The effects of the herbicide treatments were reflected in a prolonged reduction in regrowth elongation which appeared to be most pronounced for mecoprop and dicamba with mecoprop, and was still apparent in some instance 12 wks after spraying. This effect on elongation appeared to involve an interaction with drought stress and the incidence of rainfall.

L5 ANSWER 19 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1977:479533 HCAPLUS
DOCUMENT NUMBER: 87:79533
TITLE: An extended season of herbicides application for the control of Senecio jacobaea
AUTHOR(S): **Courtney, A. D.**; Johnston, R.
CORPORATE SOURCE: Field Bot. Res. Div., Dep. Agric., Belfast, UK
SOURCE: Proceedings of the British Weed Control Conference (1976), 13, Vol. 2, 611-18
CODEN: BWCPAI; ISSN: 0571-6144
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Ragwort (S. jacobaea) was controlled in 2 pastures by a variety of herbicides, such as 2,4-D amine [2008-39-1], dicamba-mecoprop mixture [58051-22-2], DMM dicamba-mecoprop-MCPA mixture [39283-71-1] etc. Timing of the application was crucial. June application gave poor result.

L5 ANSWER 20 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1976:415161 HCAPLUS
DOCUMENT NUMBER: 85:15161
TITLE: Time of herbicide application for the control of docks (Rumex obtusifolius) in a grassland conservation system
AUTHOR(S): **Courtney, A. D.**; Johnston, R. T.
CORPORATE SOURCE: Dep. Agric. Northern Ireland, Belfast, UK
SOURCE: Proceedings of the British Weed Control Conference (1974), 12, Vol. 2, 751-60
CODEN: BWCPAI; ISSN: 0571-6144
DOCUMENT TYPE: Journal
LANGUAGE: English
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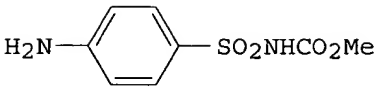

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AB The herbicides asulam (I) [3337-71-1], mecoprop [7085-19-0], and dicamba-mecoprop mixture [58051-22-2] for dock control and grass yield were most effective when applied 7-14 day intervals in July-August. Among the 3 agents tested, mecoprop had the highest yield of grass, although it was inferior in dock control.

L5 ANSWER 21 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1971:508864 HCAPLUS
DOCUMENT NUMBER: 75:108864
TITLE: Control of Rumex species in northern Ireland and the influence of herbicidal treatment on herbage yield and composition
AUTHOR(S): **Courtney, A. D.**
CORPORATE SOURCE: Minist. Agric. North. Ireland, UK
SOURCE: Proc. Brit. Weed Contr. Conf., 10th (1971), Meeting Date 1970, Volume 2, 488-94. Brit. Crop Prot. Counc.: London, Engl.
CODEN: 23NHA3
DOCUMENT TYPE: Conference
LANGUAGE: English
AB At 4 sitesin N. Ireland a range of herbicide treatments was applied to control mature Rumex species in grassland. Counts of dock shoot nos. indicated that a dicamba-mecorop mixture (1.5 lb total acid equiv (a.e.)/acre) gave the greatest degree of persistent control. Also good were mecoprop (3.2 lb a.e./ac), dichlorprop (3.2 lb a.e. acre) and asulam/mecoprop mixture (1 lb a.e. + 0.8 lb a.e. acre). Where the docks were making a considerable contribution to the dry matter yield, sample cuts of the herbage from these areas indicated that the grass content of the cuts increased when the docks were controlled but did not immediately compensate for the production of the docks.

L5 ANSWER 22 OF 22 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1971:462439 HCAPLUS
DOCUMENT NUMBER: 75:62439
TITLE: Herbicides for weed control in flax
AUTHOR(S): **Courtney, A. D.**
CORPORATE SOURCE: Minist. Agric. North. Ireland, UK
SOURCE: Proc. Brit. Weed Contr. Conf., 10th (1971), Meeting Date 1970, Volume 2, 537-44. Brit. Crop Prot. Counc.: London, Engl.
CODEN: 23NHA3
DOCUMENT TYPE: Conference
LANGUAGE: English
AB In trials of pre-and postemergence herbicides for weed control in flax, the preemergence treatments have in general proved more effective. The evidence to date suggests that the wettable powder 50% weight/weight formulation of linuron at 0.75 lb/acre, or 1.0 lb/acre on heavier soils, is safe and except in dry seasons gives satisfactory control of most species including redshank (Polygonum persicaria). Lenacil (80% weight/weight wettable powder) at 0.8 lb/acre did not give noticeably superior weed control to linuron at 0.75 lb/acre, however, the mixture of linuron + lenacil (0.5 + 0.4 lb/acre) geve generally comparable control to linuron at 0.75 lb/acre and may have an advantage with respect to crop safety as

evidenced by the one trial in 1970.

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L3            8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("ABLOOGLU ARARAT J"/AU OR
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                OR KINASE)


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L7   ANSWER 1 OF 64  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:        2005:973022  HCAPLUS
TITLE:                   p300/CBP-associated Factor Drives DEK into
                         Interchromatin Granule Clusters
AUTHOR(S):               Cleary, Joanne; Sitwala, Kajal V.; Khodadoust, Michael
                         S.; Kwok, Roland P. S.; Mor-Vaknin, Nirit; Cebrat,
                         Marek; Cole, Philip A.; Markovitz, David M.
CORPORATE SOURCE:        Department of Internal Medicine, Division of
                         Infectious Diseases, University of Michigan, Ann
                         Arbor, MI, 48109-0640, USA
SOURCE:                  Journal of Biological Chemistry (2005), 280(36),
                         31760-31767
                         CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER:               American Society for Biochemistry and Molecular
                         Biology
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   DEK is a mammalian protein that has been implicated in the pathogenesis of
     autoimmune diseases and cancer, including acute myeloid leukemia,
     melanoma, glioblastoma, hepatocellular carcinoma, and bladder cancer.  In
     addition, DEK appears to participate in multiple cellular processes,
     including transcriptional repression, mRNA processing, and chromatin
     remodeling.  Sub-nuclear distribution of this protein, with the attendant
     functional ramifications, has remained a controversial topic.  Here we
     report that DEK undergoes acetylation in vivo at lysine residues within
     the first 70 N-terminal amino acids.  Acetylation of DEK decreases its
     affinity for DNA elements within the promoter, which is consistent with
     the involvement of DEK in transcriptional repression.  Furthermore,
     deacetylase inhibition results in accumulation of DEK within
     interchromatin granule clusters (IGCs), sub-nuclear structures that
     contain RNA processing factors.  Overexpression of P/CAF acetylase drives
     DEK into IGCs, and addition of a newly developed, synthetic, cell-permeable
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P/CAF **inhibitor** blocks this movement. To our knowledge, this is the first reported example of acetylation playing a direct role in relocation of a protein to IGCs, and this may explain how DEK can function in multiple pathways that take place in distinct sub-nuclear compartments. These findings also suggest that DEK-associated malignancies and autoimmune diseases might be amenable to treatment with agents that alter acetylation.

REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:736697 HCAPLUS
TITLE: Probing conformational changes of the PCAF/GCN5 histone acetyltransferase
AUTHOR(S): Zheng, Yujun; Mamdani, Fatemah; Toptygin, Dimitri; Brand, Ludwig; Stivers, James T.; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University, Baltimore, MD, 21205, USA
SOURCE: Abstracts of Papers, 230th ACS National Meeting, Washington, DC, United States, Aug. 28-Sept. 1, 2005 (2005), BIOL-198. American Chemical Society: Washington, D. C.
CODEN: 69HFCL
DOCUMENT TYPE: Conference; Meeting Abstract; (computer optical disk)
LANGUAGE: English
AB PCAF and GCN5 are histone acetyltransferase (HAT) paralogs which play roles in the remodeling of chromatin in health and disease. Previously, a conformationally-flexible loop in the catalytic domain had been observed in the X-ray structures of GCN5 in different liganded states. Here, the conformation and dynamics of this PCAF/GCN5 alpha5-beta6 loop was investigated in solution using tryptophan fluorescence. A mutant PCAF HAT domain (PCAFWloop) was created in which the natural tryptophan (Trp514) remote from the alpha5-beta6 loop was replaced with tyrosine and a glutamate within the loop (Glu641) was substituted with tryptophan. This PCAFWloop protein showed catalytic parameters within 3-fold of those of the wild-type PCAF catalytic domain suggesting that the loop mutation was not deleterious for HAT activity. While saturating CoASH induced a 30% quenching of Trp fluorescence in PCAFWloop, binding of the high affinity **bisubstrate** analog H3-CoA-20 led to a 2-fold fluorescence increase. These different effects correlate with the different alpha5-beta6 loop conformations seen previously in X-ray structures. Based on stopped-flow fluorescence studies, H3-CoA-20 binding to PCAFWloop proceeds via a rapid association step followed by a slower conformational change involving loop movement. Fluorescence lifetime measurements support a model in which the alpha5-beta6 loop in the H3-CoA-20/PCAF complex exists in a narrower ensemble of conformations compared to the free enzyme. The relevance of loop dynamics to PCAF/GCN5 catalysis and substrate specificity is discussed.

L7 ANSWER 3 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:626824 HCAPLUS
DOCUMENT NUMBER: 143:224887
TITLE: Fluorescence Analysis of a Dynamic Loop in the PCAF/GCN5 Histone Acetyltransferase
AUTHOR(S): Zheng, Yujun; Mamdani, Fatemah; Toptygin, Dimitri; Brand, Ludwig; Stivers, James T.; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine,

Baltimore, MD, 21205, USA
SOURCE: Biochemistry (2005), 44(31), 10501-10509
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB PCAF and GCN5 are histone acetyltransferase (HAT) paralogs which play roles in the remodeling of chromatin in health and disease. Previously, a conformationally flexible loop in the catalytic domain had been observed in the X-ray structures of GCN5 in different liganded states. Here, the conformation and dynamics of this PCAF/GCN5 α5-β6 loop was investigated in solution using tryptophan fluorescence. A mutant human PCAF HAT domain (PCAFWloop) was created in which the natural tryptophan (Trp-514) remote from the α5-β6 loop was replaced with tyrosine and a glutamate within the loop (Glu-641) was substituted with tryptophan. This PCAFWloop protein exhibited catalytic parameters within 3-fold of those of the wild-type PCAF catalytic domain, suggesting that the loop mutation was not deleterious for HAT activity. While saturating CoASH induced a 30% quenching of Trp fluorescence in PCAFWloop, binding of the high-affinity **bisubstrate** analog H3-CoA-20 led to a 2-fold fluorescence increase. These different effects correlate with the different α5-β6 loop conformations seen previously in X-ray structures. On the basis of stopped-flow fluorescence studies, binding of H3-CoA-20 to PCAFWloop proceeds via a rapid association step followed by a slower conformational change involving loop movement. Time-resolved fluorescence measurements support a model in which the α5-β6 loop in the H3-CoA-20-PCAFWloop complex exists in a narrower ensemble of conformations compared to free PCAFWloop. The relevance of loop dynamics to PCAF/GCN5 catalysis and substrate specificity are discussed.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:793226 HCAPLUS
DOCUMENT NUMBER: 142:329022
TITLE: Inhibition of Epstein-Barr virus-induced growth proliferation by a nuclear antigen EBNA2-TAT peptide. [Erratum to document cited in CA140:385639]
AUTHOR(S): Farrell, Christopher J.; Lee, Jae Myun; Shin, Eui-Cheol; Cebrat, Marek; **Cole, Philip A.**; Hayward, S. Diane
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21231, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2004), 101(37), 13694
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In Materials and Methods, two latent membrane protein 1 (LMP1) primers, two β-actin primers, and one LMP1 oligonucleotide probe are mislabeled. The correct primers were used in the expts., so the conclusions are not affected. The correct sequences are as follows: PCR primers: LMP1, 5'-ATGGAACGCGACCTTGAGAG-3' and 5'-CCAAGGTACAATGCCTGTCC-3'; and β-actin, 5'-CGTGGGGCGGCCCAGGCACCA-3' and 5'-TTGGCCTTGGGGTTCAGGGGGG-3'; and oligonucleotide probe: LMP1, 5'-CCCCTCTCCTCTTCCATAGG-3'.

L7 ANSWER 5 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:761209 HCAPLUS
DOCUMENT NUMBER: 142:108224
TITLE: Tat acetylation: a regulatory switch between early and late phases in HIV transcription elongation
AUTHOR(S): Ott, Melanie; Dorr, Alexander; Hetzer-Egger, Claudia; Kaehlcke, Katrin; Schnolzer, Martina; Henklein, Peter; **Cole, Phil**; Zhou, Ming-Ming; Verdin, Eric
CORPORATE SOURCE: Gladstone Institute of Virology and Immunology, University of California, San Francisco, CA, 94103, USA
SOURCE: Novartis Foundation Symposium (2004), 259(Reversible Protein Acetylation), 182-196
CODEN: NFSYF7; ISSN: 1528-2511
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The HIV transcriptional activator Tat enhances the processivity of RNA polymerase II by recruiting the CyclinT1/CDK9 complex to the TAR RNA element. In addition, Tat synergizes with the histone acetyltransferase p300 and is acetylated by p300 at a single lysine residue (K50) in the TAR RNA binding domain. We have recently reported that this post-translational modification is necessary for the interaction and transcriptional synergy of Tat with the transcriptional coactivator PCAF. We have further studied the relevance of Tat acetylation during HIV transcription and generated antibodies specific for acetylated Tat (AcTat). Microinjection of anti-AcTat antibodies inhibited Tat-mediated transactivation in cells. Similarly, the specific p300 **inhibitor** Lys-CoA and short inhibitory RNAs specific for p300 suppressed Tat transcriptional activity. Full-length synthetic AcTat bound to TAR RNA and CyclinT1 with high affinity, but formation of the Tat-TAR-CyclinT1 ternary complex was inhibited when K50 was acetylated. Our data collectively show that Tat acetylation by p300 defines a critical step in Tat transactivation that serves to disrupt the Tat/TAR/CyclinT1 complex and helps in recruiting PCAF to the elongating RNA polymerase II.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 6 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:420513 HCAPLUS
DOCUMENT NUMBER: 141:133547
TITLE: **Bisubstrate** analogue structure-activity relationships for p300 histone acetyltransferase **inhibitors**
AUTHOR(S): Sagar, Vatsala; Zheng, Weiping; Thompson, Paul R.; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Bioorganic & Medicinal Chemistry (2004), 12(12), 3383-3390
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:133547

AB P300 and CBP are important histone acetyltransferases (HATs) that regulate gene expression and may be anti-cancer drug targets. Based on a previous lead compound, Lys-CoA, we have used solid phase synthesis to generate a series of 11 new analogs and evaluated these compds. as HAT **inhibitors.** Increased spacing between the CoA moiety and the

lysyl moiety generally decreases inhibitory potency. We have found two substituted derivs. that show about 4-fold increased potency compared to the parent compound Lys-CoA. These structure-activity studies allow for a greater understanding of the optimal requirements for potent inhibition of HAT enzymes and pave the way for a novel class of anti-cancer therapeutics.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:362593 HCAPLUS
DOCUMENT NUMBER: 141:119139
TITLE: Design, synthesis, and characterization of an ATP-peptide conjugate **inhibitor** of protein **kinase** A
AUTHOR(S): Hines, Aliya C.; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (2004), 14(11), 2951-2954
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:119139
AB An ATP-peptide conjugate was synthesized as a **bisubstrate** analog **inhibitor** of the serine/threonine **kinase** protein **kinase** A. The compound was found to be a linear, competitive **inhibitor** with respect to ATP substrate, exhibiting a Ki of 3.8 μM. The compound was noncompetitive with respect to peptide substrate. The **inhibitor** was shown to be selective for protein **kinase** A vs. the closely related protein **kinase** C as well as tyrosine **kinase** Csk. This anal. provides new evidence for the dissociative transition state of protein serine/threonine **kinases** and illustrates a simple method to convert a low affinity peptide substrate to a selective and moderately potent **inhibitor** for these enzymes.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 8 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:316124 HCAPLUS
DOCUMENT NUMBER: 140:385639
TITLE: Inhibition of Epstein-Barr virus-induced growth proliferation by a nuclear antigen EBNA2-TAT peptide
AUTHOR(S): Farrell, Christopher J.; Lee, Jae Myun; Shin, Eui-Cheol; Cebrat, Marek; **Cole, Philip A.**; Hayward, S. Diane
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21231, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2004), 101(13), 4625-4630
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Epstein-Barr virus (EBV) causes infectious mononucleosis and is associated with cancers in immunocompromised populations. Antiviral drugs targeted

against lytic viral replication have limited efficacy in these disease settings. EBV infection of peripheral blood mononuclear cells induces growth proliferation and the EBV latency Epstein-Barr virus-encoded nuclear antigen (EBNA)2 transcriptional transactivator (TAT) is essential for this response. EBNA2 targets the cellular DNA-binding protein CBF1 to mimic activated Notch signaling. A 10-aa peptide from the CBF1 interaction domain of EBNA2 was synthesized as a fusion with the protein transduction domain of HIV-1 TAT. The EBNA2-TAT peptide blocked EBNA2-CBF1 interaction in an in vitro GST affinity assay and labeling with fluorescein confirmed that the EBNA2-TAT peptide efficiently entered cultured B cells. Neither EBNA2-TAT, nor a mutant peptide with a 2-aa substitution that was unable to block the EBNA2-CBF1 interaction, significantly affected the growth of non-EBNA2-expressing EBV(-) B cells or Burkitt's lymphoma Akata cells. However, treatment of an EBV-immortalized lymphoblastoid cell line with the EBNA2-TAT peptide stopped cell growth and reduced cell viability. RT-PCR analyses of gene expression in the peptide-treated lymphoblastoid cell line cultures revealed that EBNA2-TAT treatment down-regulated the EBNA2-responsive viral LMP1 and LMP2 genes and cellular CD23, intercellular adhesion mol. 1, BATF, and Cdk1 genes while up-regulating expression of the cyclin-dependent **kinase inhibitor** p21. EBV-induced outgrowth of B cells from cultured peripheral blood mononuclear cells was also blocked in a dose-responsive manner by the EBNA2-TAT peptide. This study suggests that cell-permeable EBNA2 peptides may have potential as novel anti-EBV therapeutics.

REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 9 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:301649 HCAPLUS
DOCUMENT NUMBER: 141:309475
TITLE: Selective HAT **inhibitors** as mechanistic tools for protein acetylation
AUTHOR(S): Zheng, Yujun; Thompson, Paul R.; Cebrat, Marek; Wang, Ling; Devlin, Meghann K.; Alani, Rhoda M.; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21218, USA
SOURCE: Methods in Enzymology (2004), 376(Chromatin and Chromatin Remodeling Enzymes, Part B), 188-199
CODEN: MENZAU; ISSN: 0076-6879
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Histone acetyltransferases (HATs) regulate gene expression by the targeted acetylation of histones and other proteins. The use of selective HAT **inhibitors** was introduced as mechanistic tools to probe the catalytic features of HATs and their roles in various cellular pathways. The design, synthesis, and applications of these **inhibitors** in different biol. contexts are described. It is hoped that HAT **inhibitors** might ultimately serve useful clin. role in the treatment of cancer and other diseases.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:254163 HCAPLUS
DOCUMENT NUMBER: 140:387787
TITLE: Regulation of the p300 HAT domain via a novel

activation loop
AUTHOR(S): Thompson, Paul R.; Wang, Dongxia; Wang, Ling; Fulco, Marcella; Pediconi, Natalia; Zhang, Dianzheng; An, Woojin; Ge, Qingyuan; Roeder, Robert G.; Wong, Jiemin; Levrero, Massimo; Sartorelli, Vittorio; Cotter, Robert J.; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Nature Structural & Molecular Biology (2004), 11(4), 308-315
CODEN: NSMBCU; ISSN: 1545-9993
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The transcriptional coactivator p300 is a histone acetyltransferase (HAT) whose function is critical for regulating gene expression in mammalian cells. However, the mol. events that regulate p300 HAT activity are poorly understood. We evaluated autoacetylation of the p300 HAT protein domain to determine its function. Using expressed protein ligation, the p300 HAT protein domain was generated in hypoacetylated form and found to have reduced catalytic activity. This basal catalytic rate was stimulated by autoacetylation of several key lysine sites within an apparent activation loop motif. This post-translational modification and catalytic regulation of p300 HAT activity is conceptually analogous to the activation of most protein **kinases** by autophosphorylation. We therefore propose that this autoregulatory loop could influence the impact of p300 on a wide variety of signaling and transcriptional events.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 11 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:958238 HCAPLUS
DOCUMENT NUMBER: 140:89809
TITLE: Conversion of a Tyrosine **Kinase** Protein Substrate to a High Affinity Ligand by ATP Linkage
AUTHOR(S): Shen, Kui; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Journal of the American Chemical Society (2003), 125(52), 16172-16173
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:89809
AB Protein **kinases** often show low affinity for their protein substrates, which makes it difficult to study **kinase**-substrate interactions. Here, the authors show using expressed protein ligation with the signaling protein Src that it is feasible to install a covalently linked ATP moiety into the tail of Src, generating a semisynthetic protein with a high affinity for its cognate tyrosine **kinase**, Csk. It is also established that this Src-ATP conjugate can be used to selectively pull down Csk from a complex protein mixture This work outlines a general strategy for identifying an unknown **kinase** that is responsible for the phosphorylation of a protein substrate on a site of interest.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 12 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:829216 HCAPLUS
DOCUMENT NUMBER: 140:195198
TITLE: Protein tyrosine **kinases** Src and Csk: a tail's tale
AUTHOR(S): **Cole, Philip A.**; Shen, Kui; Qiao, Yingfeng; Wang, Dongxia
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Current Opinion in Chemical Biology (2003), 7(5), 580-585
CODEN: COCBF4; ISSN: 1367-5931
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review and discussion. Csk and Src are 2 protein tyrosine **kinases** with similar amino acid sequences but very different structures and functions. Csk catalyzes a tail phosphorylation reaction on Src and thereby restrains Src's activity and oncogenic potential. Comparative anal. of the domain interactions in these enzymes provides a lesson in signaling diversity and mechanisms of enzyme regulation. The mol. basis of the specificity of Csk targeting the Src tail appears to involve both local and long-range interactions and illustrates the complexity of selective targeting in post-translational modification.
REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 13 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:673327 HCAPLUS
DOCUMENT NUMBER: 139:334684
TITLE: Novel **bisubstrate** analog **inhibitors** of serotonin N-acetyltransferase: the importance of being neutral
AUTHOR(S): Zheng, Weiping; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Bioorganic Chemistry (2003), 31(5), 398-411
CODEN: BOCMBM; ISSN: 0045-2068
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 139:334684
AB Linker modified novel **bisubstrate** analog **inhibitors** for serotonin N-acetyltransferase (arylalkylamine N-acetyltransferase, AANAT) have been designed and synthesized. Examination of these **inhibitors** with AANAT in vitro suggested the following points: (i) linker hydrogen bonding makes only modest contributions to the affinity of **bisubstrate** analog **inhibitors** studied; (ii) greater than or equal to four methylene groups between the indole and the CoA (CoASH) moieties are required for a **bisubstrate** analog **inhibitor** to achieve strong AANAT inhibition; (iii) the AANAT active site appears not to accommodate pos. charged linkers as well as neutral ones; and (iv) substrate amine pKa depression may constitute one strategy for AANAT substrate recognition and catalysis. The results reported here have enhanced our understanding of AANAT substrate recognition/catalysis, and are important for novel **inhibitor** design. Since AANAT belongs to the GCN5-related N-acetyltransferase (GNAT) superfamily, our exptl. strategies should find applications for other acetyltransferases.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 14 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:631384 HCAPLUS
TITLE: Chemical approaches to sorting out protein phosphorylation
AUTHOR(S): **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University, Baltimore, MD, 21205, USA
SOURCE: Abstracts of Papers, 226th ACS National Meeting, New York, NY, United States, September 7-11, 2003 (2003), COMP-224. American Chemical Society: Washington, D. C.
CODEN: 69EKY9
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Reversible protein phosphorylation represents a major mechanism for cell signal transduction. We will summarize a few recent technologies developed and applied in our lab to understand the function of protein **kinases** in various contexts. In particular, we will discuss the design and application of **bisubstrate** analogs as protein **kinase inhibitors**, the chemical rescue of mutant tyrosine **kinases**, and the use of expressed protein ligation in protein phosphorylation anal.

L7 ANSWER 15 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:624989 HCAPLUS
DOCUMENT NUMBER: 139:257962
TITLE: Acetylation of Tat defines a cyclinT1-independent step in HIV transactivation
AUTHOR(S): Kaehicke, Katrin; Dorr, Alexander; Hetzer-Egger, Claudia; Kiermer, Veronique; Henklein, Peter; Schnoelzer, Martina; Loret, Erwann; **Cole, Philip A.**; Verdin, Eric; Ott, Melanie
CORPORATE SOURCE: Deutsches Krebsforschungszentrum, Heidelberg, D-69120, Germany
SOURCE: Molecular Cell (2003), 12(1), 167-176
CODEN: MOCEFL; ISSN: 1097-2765
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The HIV transcriptional activator Tat is acetylated by p300 at a single lysine residue in the TAR RNA binding domain. We have generated monoclonal and polyclonal antibodies specific for the acetylated form of Tat (AcTat). Microinjection of anti-AcTat antibodies inhibited Tat-mediated transactivation in cells. Similarly, the p300 **inhibitor** Lys-CoA and siRNA specific for p300 suppressed Tat transcriptional activity. Full-length synthetic AcTat bound to TAR RNA with the same affinity as unacetylated Tat, but formation of a Tat-TAR-CyclinT1 ternary complex was completely inhibited in the presence of AcTat. We propose that Tat acetylation may help in dissociating the Tat cofactor CyclinT1 from TAR RNA and serve to transfer Tat onto the elongating RNA polymerase II.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 16 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:500681 HCAPLUS
DOCUMENT NUMBER: 140:52742

TITLE: Synthesis and analysis of potential prodrugs of coenzyme A analogues for the inhibition of the histone acetyltransferase p300
AUTHOR(S): Cebrat, Marek; Kim, Cheol M.; Thompson, Paul R.; Daugherty, Matthew; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, School of Medicine, Johns Hopkins University, Baltimore, MD, 21205, USA
SOURCE: Bioorganic & Medicinal Chemistry (2003), 11(15), 3307-3313
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Lys-CoA (1) is a selective **inhibitor** of p300 histone acetyltransferase (HAT) but shows poor pharmacokinetic properties because of its multiply charged phosphates. In an effort to overcome this limitation, truncated derivs. of 1 were designed, synthesized and tested as p300HAT **inhibitors** as well as substrates for the CoA biosynthetic bifunctional enzyme phosphopantetheine adenylyltransferase-dephospho-CoA **kinase** (PPAT/DPCK). Lys-pantetheine (3) and Lys-phosphopantetheine (2) showed no detectable p300HAT inhibition whereas 3'-dephospho-Lys-CoA (5) was a modest p300 **inhibitor** with IC50 of 1.6 μM (compared to IC50 of .apprx.50 nM for 1 blocking p300). Compound 2 was shown to be an efficient substrate for PPAT whereas 5 was a very poor DPCK substrate. Further anal. with 3'-dephospho-Me-SCoA (7) indicated that DPCK shows relatively narrow capacity to accept substrates with sulfur substitution. While these results suggest that truncated derivs. of 1 will be of limited value as lead agents for p300 blockade in vivo, they augur well for prodrug versions of CoA analogs that do not require 3'-phosphate substitution for efficient binding to their targets, such as the GCN-5 related N-acetyltransferases.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 17 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:106602 HCAPLUS
DOCUMENT NUMBER: 139:65326
TITLE: The Role of C-terminal Tyrosine Phosphorylation in the Regulation of SHP-1 Explored via Expressed Protein Ligation
AUTHOR(S): Zhang, Zhongsen; Shen, Kui; Lu, Wei; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Journal of Biological Chemistry (2003), 278(7), 4668-4674
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The protein tyrosine phosphatase SHP-1 plays a variety of roles in the "neg." regulation of cell signaling. The mol. basis for the regulation of SHP-1 is incompletely understood. Whereas SHP-1 has previously been shown to be phosphorylated on two tail tyrosine residues (Tyr536 and Tyr564) by several protein tyrosine **kinases**, the effects of these phosphorylation events have been difficult to address because of the intrinsic instability of the linkages within a protein tyrosine

phosphatase. Using expressed protein ligation, we have generated semisynthetic SHP-1 proteins containing phosphotyrosine mimetics at the Tyr536 and Tyr564 sites. Two phosphonate analogs were installed, phosphonomethylenephenylalanine (Pmp) and difluorophosphonomethylenephenyl alanine (F2Pmp). Incorporation of Pmp at the 536 site led to 4-fold stimulation of the SHP-1 tyrosine phosphatase activity whereas incorporation at the 564 site led to no effect. Incorporation of F2Pmp at the 536 site led to 8-fold stimulation of the SHP-1 tyrosine phosphatase activity and 1.6-fold at the 564 site. A combination of size exclusion chromatog., phosphotyrosine peptide stimulation studies, and site-directed mutagenesis led to the structural model in which tyrosine phosphorylation at the 536 site engages the N-Src homol. 2 domain in an intramol. fashion relieving basal inhibition. In contrast, tyrosine phosphorylation at the 564 site has the potential to engage the C-Src homol. 2 domain intramolecularly, which can modestly and indirectly influence catalytic activity. The finding that phosphonate modification at each of the 536 and 564 sites can promote interaction with the Grb2 adaptor protein indicates that the intramol. interactions fostered by post-translational modifications of tyrosine are not energetically strong and susceptible to intermol. competition.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 18 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:859524 HCAPLUS
DOCUMENT NUMBER: 138:87174
TITLE: Down-regulation of p300/CBP histone acetyltransferase activates a senescence checkpoint in human melanocytes
AUTHOR(S): Bandyopadhyay, Debdutta; Okan, Nihal A.; Bales, Elise; Nascimento, Lucia; **Cole, Philip A.**; Medrano, Estela E.
CORPORATE SOURCE: Huffington Center on Aging and Department of Molecular and Cellular Biology and Dermatology, Baylor College of Medicine, Houston, TX, 77030, USA
SOURCE: Cancer Research (2002), 62(21), 6231-6239
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The histone acetyltransferases p300 and cAMP-responsive element-binding protein-binding protein (CBP) are required for the execution of critical biol. functions such as proliferation, differentiation, and apoptosis. Both proteins are believed to regulate the activity of a large number of general and cell-specific transcription factors. Here we demonstrate a dramatic decrease in the total cellular levels of p300 and CBP with increasing population doublings of human normal melanocytes. We show that one consequence of p300 depletion is transcriptional down-regulation of the cyclin E gene, caused by deacetylation of histones at its promoter. The cyclin E promoter was activated by p300 and the histone deacetylase **inhibitor** trichostatin A. Conversely, the cyclin E promoter was repressed by wild-type Retinoblastoma tumor suppressor p105 protein (pRB) and by a dominant neg. p300 mutant (DN p300) that lacks histone acetyltransferase activity. We also provide evidence of the alternative recruitment of p300 and histone deacetylase 1 to the cyclin E promoter in proliferating and senescent melanocytes, resp. The biol. significance of these results was established by showing that block of p300 activity by overexpression of DN p300 or by Lys-CoA, a specific chemical **inhibitor** of p300, resulted in growth inhibition, down-regulation of cyclin E, and activation of the senescence-associated β-galactosidase marker in human melanocytes and melanoma cells. Together, these results

provide evidence for the essential role of p300 in the regulation of proliferation and senescence in cells from melanocytic origin.
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 19 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:859143 HCAPLUS
DOCUMENT NUMBER: 138:200902
TITLE: Structure of the GCN5 histone acetyltransferase bound to a **bisubstrate inhibitor**
AUTHOR(S): Poux, Arienne N.; Cebrat, Marek; Kim, Cheol M.; **Cole, Philip A.**; Marmorstein, Ronen
CORPORATE SOURCE: The Wistar Institute, and Department of Chemistry, University of Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2002), 99(22), 14065-14070
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Histone acetyltransferases (HATs) use acetyl CoA to acetylate target lysine residues within histones and other transcription factors, such as the p53 tumor suppressor, to promote gene activation. HAT enzymes fall into subfamilies with divergence in sequence and substrate preference. Several HAT proteins have been implicated in human cancer. We have previously reported on the preparation of peptide-CoA conjugate **inhibitors** with distinct specificities for the p300/CBP [cAMP response element binding protein (CREB)-binding protein] or GCN5 HAT subfamilies. Here we report on the crystal structure of the GCN5 HAT bound to a peptide-CoA conjugate containing CoA covalently attached through an isopropionyl linker to Lys-14 of a 20-aa N-terminal fragment of histone H3. Surprisingly, the structure reveals that the H3 portion of the **inhibitor** is bound outside of the binding site for the histone substrate and that only five of the 20 aa residues of the **inhibitor** are ordered. Rearrangements within the C-terminal region of the GCN5 protein appear to mediate this peptide displacement. Mutational and enzymic data support the hypothesis that the observed structure corresponds to a late catalytic intermediate. The structure also provides a structural scaffold for the design of HAT-specific **inhibitors** that may have therapeutic applications for the treatment of HAT-mediated cancers.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 20 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:798434 HCAPLUS
DOCUMENT NUMBER: 138:102774
TITLE: Substrate Conformational Restriction and CD45-catalyzed Dephosphorylation of Tail Tyrosine-phosphorylated Src Protein
AUTHOR(S): Wang, Dongxia; Esselman, Walter J.; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Journal of Biological Chemistry (2002), 277(43), 40428-40433
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular

Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hydrolysis of the tail phosphotyrosine in Src family members is catalyzed by the protein-tyrosine phosphatase CD45, activating Src family-related signaling pathways. Using purified recombinant phospho-Src (P-Src) (amino acid residues 83-533) and purified recombinant CD45 catalytic (cytoplasmic) domain (amino acid residues 565-1268), we have analyzed the kinetic behavior of dephosphorylation. A time course of phosphatase activity showed the presence of a burst phase. By varying the concentration of P-Src, it was shown that the amplitude of this burst phase increased linearly with respect to P-Src concentration Approx. 2% of P-Src was shown to be rapidly dephosphorylated followed by a slower linear phase. A P-Src protein substrate containing a functional point mutation in the Src homol. domain 2 (SH2) led to more rapid dephosphorylation catalyzed by CD45, and this reaction showed only a single linear kinetic phase. These results were interpreted in terms of a model in which P-Src exists in a relatively slow dynamic equilibrium between "closed" and "open" conformational forms. Combined mutations in the SH2 and SH3 domain or the addition of an SH3 domain ligand peptide enhanced the accessibility of P-Src to CD45 by biasing P-Src to a more open form. Consistent with this model, a phosphotyrosine peptide that behaved as an SH2 domain binding ligand showed .apprx.100-fold greater affinity for unphosphorylated Src vs. P-Src. Surprisingly, P-Src possessing combined SH3 and SH2 functional inactivating point mutations was dephosphorylated by CD45 more slowly compared with P-Src completely lacking SH3 and SH2 domains. Addnl. data suggest that the SH3 and SH2 domains can inhibit accessibility of the P-Src tail to CD45 by interactions other than direct phosphotyrosine binding by the SH2 domain. Taken together, these results suggest how activation of Src family member signaling pathways by CD45 may be influenced by the presence or absence of ligand interactions remote from the tail.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 21 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:794219 HCAPLUS
DOCUMENT NUMBER: 137:307009
TITLE: Chemical ligation of proteins via amide bond through transthioesterification/cleavage reaction for NMR and protein-chip applications
INVENTOR(S): Muir, Tom W.; **Cole, Philip A.**; Friedman, Jeffrey M.; Sondhi, Dolan; Severinov, Konstantine
PATENT ASSIGNEE(S): The Rockefeller University, USA
SOURCE: U.S. Pat. Appl. Publ., 35 pp., Cont. of U.S. Ser. No. 191,890.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2002151006	A1	20021017	US 2001-904117		20010712
US 6875594	B2	20050405			
PRIORITY APPLN. INFO.:			US 1997-65391P	P	19971113
			US 1998-93990P	P	19980724
			US 1998-191890	B1	19981113

AB The present invention relates to methods for chemical ligating two oligopeptides end to end with an amide bond, wherein at least one of the oligopeptides is a product of recombinant expression. The present invention further relates to segmental isotopic labeling of recombinant protein domains, and segmental expression of recombinant protein domains or subunits and subsequent ligation and uses thereof. The present invention also relates to use of these methods for producing protein-chip compns. and uses thereof. The present invention provides a method of cleaving a recombinantly expressed protein from an intein and ligating the protein to a peptide containing an N-terminal cysteine having an unoxidized sulfhydryl side chain which comprises contacting the protein with the peptide in a reaction solution comprising a conjugated thiophenol, thereby forming a C-terminal thioester of the recombinant protein which spontaneously rearranges intramolecularly to form an amide bond linking the protein to the peptide. Accordingly, this invention relates to a method of ligating a recombinantly expressed protein to an oligopeptide. Utilizing a particular reagent, i.e., a thiophenol, to cleave the recombinantly expressed protein from its manufacturing process, and in the presence of the oligopeptide to which it is to be ligated, the desired ligation reaction occurs without the necessity for conversion to the necessary α-thioester prior to ligation with the oligopeptide. It is also a further object of the present invention to provide a method for NMR spectroscopy using proteins segmentally labeled by the provided method. Appending a phosphotyrosine tail to Csk, highly homologous to Src but lacks a C-terminal tyrosine-containing tail, resulted in a new conformation involving an intramol. interaction between the SH2 domain and the tail phosphotyrosine. This report also describes the development of procedures which for the first time allow two folded recombinant protein domains to be efficiently linked together by in vitro chemical ligation reactions. This strategy was used to prepare NMR quantities of the Abelson protein tyrosine **kinase** regulatory apparatus, Abl-SH(32), in which only one domain was uniformly labeled with 15N. The in vitro chemical ligation strategy called for the generation of a recombinant Abl-SH3 domain activated at its C-terminus as a-thioester, and a recombinant Abl-SH2 domain containing an N-terminal cysteine residue. These two folded protein domains, when combined under physiol. conditions;, chemoselectively reacted via the well established native chemical ligation reaction to form an amide linkage at the ligation junction.

L7 ANSWER 22 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:618077 HCAPLUS
TITLE: Histone acetyltransferases: From structure to function and synthetic **inhibitors**
AUTHOR(S): Marmorstein, Ronen; Clements, Adrienne; Poux, Adrienne; Yan, Yuan; Cebrat, Marek; Kim, Cheol M.; Lo, Wan-Sheng; Berger, Shelly; **Cole, Philip A.**
CORPORATE SOURCE: Structural Biology Program, The Wistar Institute, Philadelphia, PA, 19104-4268, USA
SOURCE: Abstracts of Papers, 224th ACS National Meeting, Boston, MA, United States, August 18-22, 2002 (2002), MEDI-225. American Chemical Society: Washington, D. C.
CODEN: 69CZPZ
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Histone acetyltransferases (HATs) acetylate specific lysine residues in histones to promote gene activation, and the deregulation of several HATs has been implicated in human cancer making them attractive therapeutic targets. We have determined structures of members of the Gcn5/PCAF and MYST subfamily of HATs and have characterized their function in vitro to probe

the mechanism of histone substrate binding specificity and catalysis. Our studies show that HATs contain a structurally conserved domain that mediates CoA-binding and catalysis, although we find that the mode of catalysis differs dramatically between the Gcn5/PCAF and MYST HATs. The two HAT subfamilies contain a similar structural scaffold for histone binding and sequence divergence within this scaffold appears to contribute to histone substrate specificity. The structure of Gcn5 bound to a **bisubstrate inhibitor** provides further insights into the mechanism of catalysis by these enzymes and provides a scaffold for the design of HAT-specific **inhibitors.**

L7 ANSWER 23 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:471979 HCAPLUS
DOCUMENT NUMBER: 137:195985
TITLE: Csk, a critical link of G protein signals to actin cytoskeletal reorganization
AUTHOR(S): Lowry, William E.; Huang, Jianyun; Ma, Yong-Chao; Ali, Shariq; Wang, Dongxia; Williams, Daniel M.; Okada, Masato; **Cole, Philip A.**; Huang, Xin-Yun
CORPORATE SOURCE: Department of Physiology, Weill Medical College, Cornell University, New York, NY, 10021, USA
SOURCE: Developmental Cell (2002), 2(6), 733-744
CODEN: DCEEBE; ISSN: 1534-5807
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Heterotrimeric G proteins can signal to reorganize the actin cytoskeleton, but the mechanism is unclear. Here we report that, in tyrosine **kinase** Csk-deficient mouse embryonic fibroblast cells, G protein (Gβγ, Gα12, Gα13, and Gαq)-induced, and G protein-coupled receptor-induced, actin stress fiber formation was completely blocked. Reintroduction of Csk into Csk-deficient cells restored the G protein-induced actin stress fiber formation. Chemical rescue expts. with catalytic mutants of Csk demonstrated that the catalytic activity of Csk was required for this process. Furthermore, we uncovered that Gβγ can both translocate Csk to the plasma membrane and directly increase Csk **kinase** activity. Our genetic and biochem. studies demonstrate that Csk plays a critical role in mediating G protein signals to actin cytoskeletal reorganization.
REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 24 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:435236 HCAPLUS
DOCUMENT NUMBER: 137:136733
TITLE: Serotonin N-acetyltransferase: Mechanism and inhibition
AUTHOR(S): Zheng, Weiping; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Current Medicinal Chemistry (2002), 9(12), 1187-1199
CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 76 refs. Serotonin N-acetyltransferase (arylalkylamine N-acetyltransferase) (I) catalyzes the rate-limiting step in the biosynthesis of the circadian hormone, melatonin, from serotonin. Although melatonin was identified 40 yr ago, relatively little is known

about its (patho)physiol. roles, and a solid scientific foundation is still lacking for most therapeutic applications currently claimed for melatonin. The development of potent, specific, and cell-permeable **inhibitors** for I should constitute an important strategy to address these issues. These **inhibitors** are also potential therapeutics for various sleep/mood disorders. This review focuses on the efforts toward developing in vitro and in vivo I **inhibitors**, including basic mechanistic studies on I, which have played an important role in design.

REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 25 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:404517 HCAPLUS
DOCUMENT NUMBER: 137:151733
TITLE: Investigation of the roles of catalytic residues in serotonin N-acetyltransferase
AUTHOR(S): Scheibner, Kara A.; De Angelis, Jacqueline; Burley, Stephen K.; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Journal of Biological Chemistry (2002), 277(20), 18118-18126
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Serotonin N-acetyltransferase (arylalkylamine N-acetyltransferase (AANAT)) is a critical enzyme in the light-mediated regulation of melatonin production and circadian rhythm. It is a member of the GNAT (GCN-5-related N-acetyltransferase) superfamily of enzymes, which catalyze a diverse array of biol. important acetyl transfer reactions from antibiotic resistance to chromatin remodeling. In this study, the authors probed the functional properties of two histidines (His 120 and His 122) and a tyrosine (Tyr 168) postulated to be important in the mechanism of AANAT based on prior x-ray structural and biochem. studies. Using a combination of steady-state kinetic measurements of microviscosity effects and pH dependence on the H122Q, H120Q, and H120Q/H122Q AANAT mutants, the authors show that His 122 (with an apparent pKa of 7.3) contributes .apprx.6-fold to the acetyltransferase chemical step as either a remote catalytic base or hydrogen bond donor. Furthermore, His 120 and His 122 appear to contribute redundantly to this function. By anal. of the Y168F AANAT mutant, it was demonstrated that Tyr 168 contributes .apprx.150-fold to the acetyltransferase chemical step and is responsible for the basic limb of the pH-rate profile with an apparent (subnormal) pKa of 8.5. Paradoxically, Y168F AANAT showed 10-fold enhanced apparent affinity for acetyl-CoA despite the loss of a hydrogen bond between the Tyr phenol and the CoA sulfur atom. The x-ray crystal structure of Y168F AANAT bound to a **bisubstrate** analog **inhibitor** showed no significant structural perturbation of the enzyme compared with the wild-type complex, but revealed the loss of dual **inhibitor** conformations present in the wild-type complex. Taken together with kinetic measurements, these crystallog. studies allow the authors to propose the relevant structural conformations related to the distinct alkyltransferase and acetyltransferase reactions catalyzed by AANAT. These findings have significant implications for understanding GNAT catalysis and the design of potent and selective **inhibitors.**

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 26 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:335834 HCAPLUS
DOCUMENT NUMBER: 137:241811
TITLE: Retinoids and carnosol suppress cyclooxygenase-2 transcription by CREB-binding protein/p300-dependent and -independent mechanisms
AUTHOR(S): Subbaramaiah, Kotha; **Cole, Philip A.**; Dannenberg, Andrew J.
CORPORATE SOURCE: Department of Medicine, New York Presbyterian Hospital-Cornell and Strang Cancer Prevention Center, New York, NY, 10021, USA
SOURCE: Cancer Research (2002), 62(9), 2522-2530
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Treatment with retinoic acid (RA) or carnosol, two structurally unrelated compds. with anticancer properties, inhibited phorbol ester (PMA)-mediated induction of activator protein-1 (AP-1) activity and cyclooxygenase-2 (COX-2) expression in human mammary epithelial cells. The induction of COX-2 transcription by PMA was mediated by increased binding of AP-1 to the cAMP response element (CRE) of the COX-2 promoter. Inhibition of the histone acetyltransferase activity of CREB-binding protein (CBP)/p300 blocked the induction of COX-2 by PMA. Treatment with carnosol but not RA blocked increased binding of AP-1 to the COX-2 promoter. Because AP-1 binding was unaffected by RA, we investigated whether RA inhibited COX-2 transcription via effects on the coactivator CBP/p300. Treatment with RA stimulated an interaction between RA receptor-α and CBP/p300; a corresponding decrease in the interaction between CBP/p300 and c-Jun was observed Importantly, overexpressing CBP/p300 or dominant-neg. RA receptor-α relieved the suppressive effect of RA on PMA-mediated stimulation of the COX-2 promoter. To elucidate the mechanism by which carnosol inhibited COX-2 transcription, its effects on protein **kinase** C (PKC) signaling were determined Carnosol but not RA inhibited the activation of PKC, ERK1/2, p38, and c-Jun NH2-terminal **kinase** mitogen-activated protein **kinase.** Overexpressing c-Jun but not CBP/p300 reversed the suppressive effect of carnosol on PMA-mediated stimulation of COX-2 promoter activity. Thus, RA acted by a receptor-dependent mechanism to limit the amount of CBP/p300 that was available for AP-1-mediated induction of COX-2. By contrast, carnosol inhibited the induction of COX-2 by blocking PKC signaling and thereby the binding of AP-1 to the CRE of the COX-2 promoter. Taken together, these results show that small mols. can block the activation of COX-2 transcription by distinct mechanisms.
REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 27 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:326837 HCAPLUS
DOCUMENT NUMBER: 137:75166
TITLE: Proton Demand Inversion in a Mutant Protein Tyrosine **Kinase** Reaction
AUTHOR(S): Williams, Daniel M.; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Journal of the American Chemical Society (2002),

124(21), 5956-5957
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In contrast to previous studies that have shown that the neutral phenol serves as the nucleophile for WT Csk-promoted phosphorylation of a tyrosine-containing substrate, the phenolate ion acts as primary nucleophile for the D314N Csk-catalyzed reaction. Rate comparisons of D314N Csk-promoted phosphotransfer using a series of fluorotyrosine-containing peptide substrates reveal a near zero βnuc, consistent with a dissociative mechanism of phosphotransfer. These combined results argue against a hydroxy nucleophile-to-phosphate proton transfer occurring prior to an associative transition state of phosphoryl transfer.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 28 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:271977 HCAPLUS
DOCUMENT NUMBER: 136:310176
TITLE: Preparation of peptide CoA conjugates as **inhibitors** of histone acetyltransferases (HATs)
INVENTOR(S): **Cole, Philip A.**; Soccio, Raymond E.; Lau, Ontario D.; Khalil, Ehab M.; Kundu, Tapas K.; Roeder, Robert G.
PATENT ASSIGNEE(S): The Rockefeller University, USA
SOURCE: U.S., 20 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6369030	B1	20020409	US 1999-451034	19991129
PRIORITY APPLN. INFO.:			US 1999-451034	19991129

OTHER SOURCE(S): MARPAT 136:310176
AB The design, synthesis, and application of peptide CoA conjugates as selective HAT **inhibitors** for the transcription factors p300 and PCAF are described. Two **inhibitors** (Lys-CoA for p300, H3-CoA-20 for PCAF) were found to be potent (IC50 .apprx. 0.5 μM) and selective (.apprx. 200-fold) in blocking p300 and PCAF HAT activity. These **inhibitors** were used to show quant. that PCAF and p300 display additive but not synergistic HAT activity when present in mixts. Lys-CoA was used to directly demonstrate the importance of p300 HAT activity in enhancing chromatin template mediated transcription in vitro.
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 29 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:207764 HCAPLUS
DOCUMENT NUMBER: 137:17102
TITLE: X-ray Crystallographic Studies of Serotonin N-acetyltransferase Catalysis and Inhibition
AUTHOR(S): Wolf, Eva; De Angelis, Jacqueline; Khalil, Ehab M.; **Cole, Philip A.**; Burley, Stephen K.
CORPORATE SOURCE: Laboratories of Molecular Biophysics, The Rockefeller University, New York, NY, 10021, USA

SOURCE: Journal of Molecular Biology (2002), 317(2), 215-224
CODEN: JMOBAK; ISSN: 0022-2836
PUBLISHER: Elsevier Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The structure of serotonin N-acetyltransferase (also known as arylalkylamine N-acetyltransferase; AANAT) bound to a potent **bisubstrate** analog **inhibitor** has been determined at 2.0 Å resolution using a two-edge (Se, Br) multiwavelength anomalous diffraction (MAD) experiment This acetyl-CoA dependent enzyme is a member of the GCN5-related family of N-acetyltransferases (GNATs), which share four conserved sequence motifs (A-D). In serotonin N-acetyltransferase, motif A adopts an α/β conformation characteristic of the phylogenetically invariant cofactor binding site seen in all previously characterized GNATs. Motif B displays a significantly lower level of conservation among family members, giving rise to a novel α/β structure for the serotonin binding slot. Utilization of a brominated CoA-S-acetyl-tryptamine-**bisubstrate** analog **inhibitor** and the MAD method permitted conclusive identification of two radically different conformations for the tryptamine moiety in the catalytic site (cis and trans). A second high-resolution x-ray structure of the enzyme bound to a **bisubstrate** analog **inhibitor**, with a longer tether between the acetyl-CoA and tryptamine moieties, demonstrates only the trans conformation. Given a previous proposal that AANAT can catalyze an alkyltransferase reaction in a conformationally altered active site relative to its acetyltransferase activity, it is possible that the two conformations of the **bisubstrate** analog observed crystallog. correspond to these alternative reaction pathways. Our findings may ultimately lead to the design of analogs with improved AANAT inhibitory properties for in vivo applications.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 30 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:902976 HCAPLUS
DOCUMENT NUMBER: 136:181211
TITLE: CBP/p300 and muscle differentiation: no HAT, no muscle
AUTHOR(S): Polesskaya, A.; Naguibneva, I.; Fritsch, L.; Duquet, A.; Ait-Si-Ali, S.; Robin, P.; Vervisch, A.; Pritchard, L. L.; **Cole, P.**; Harel-Bellan, A.
CORPORATE SOURCE: CNRS UPR 9079, Institut Andre Lwoff, Villejuif, 94800, Fr.
SOURCE: EMBO Journal (2001), 20(23), 6816-6825
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Terminal differentiation of muscle cells follows a precisely orchestrated program of transcriptional regulatory events at the promoters of both muscle-specific and ubiquitous genes. Two distinct families of transcriptional co-activators, GCN5/PCAF and CREB-binding protein (CBP)/p300, are crucial to this process. While both possess histone acetyl-transferase (HAT) activity, previous studies have failed to identify a requirement for CBP/p300 HAT function in myogenic differentiation. We have addressed this issue directly using a chemical **inhibitor** of CBP/p300 in addition to a neg. transdominant mutant. Our results clearly demonstrate that CBP/p300 HAT activity is critical for myogenic terminal differentiation. Furthermore, this requirement is restricted to a subset of events in the differentiation program: cell fusion and specific gene expression. These data help to define the

requirements for enzymic function of distinct coactivators at different stages of the muscle cell differentiation program.
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 31 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:859343 HCAPLUS
DOCUMENT NUMBER: 136:98372
TITLE: Novel Mechanism of Regulation of the Non-receptor Protein Tyrosine **Kinase** Csk: Insights from NMR Mapping Studies and Site-directed Mutagenesis
AUTHOR(S): Shekhtman, Alexander; Ghose, Ranajeet; Wang, Dongxia; **Cole, Philip A.**; Cowburn, David
CORPORATE SOURCE: The Rockefeller University, New York, NY, 10021-6399, USA
SOURCE: Journal of Molecular Biology (2001), 314(1), 129-138
CODEN: JMOBAK; ISSN: 0022-2836
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Csk (C-terminal Src **kinase**), a protein tyrosine **kinase**, consisting of the Src homol. 2 and 3 (SH2 and SH3) domains and a catalytic domain, phosphorylates the C-terminal tail of Src-family members, resulting in down-regulation of the Src family **kinase** activity. The Src family **kinases** share 37 % homol. with Csk but, unlike Src-family **kinases**, the catalytic domain of Csk alone is weakly active and can be stimulated in trans by interacting with the Csk-SH3 domain, suggesting a mode of intra-domain regulation different from that of Src family **kinases.** The structural determinants of this intermol. interaction were studied by NMR and site-directed mutagenesis techniques. Chemical shift perturbation of backbone nuclei (H' and 15N) has been used to map the Csk catalytic domain binding site on the Csk-SH3. The exptl. determined interaction surface includes three structural elements: the N-terminal tail, a small part of the RT-loop, and the C-terminal SH3-SH2 linker. Site-directed mutagenesis revealed that mutations in the SH3-SH2 linker of the wild-type Csk decrease Csk **kinase** activity up to fivefold, whereas mutations in the RT-loop left Csk **kinase** activity largely unaffected. We conclude that the SH3-SH2 linker plays a major role in the activation of the Csk catalytic domain. (c) 2001 Academic Press.
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 32 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:839353 HCAPLUS
DOCUMENT NUMBER: 136:336067
TITLE: Chromatin-dependent cooperativity between constitutive and inducible activation domains in CREB
AUTHOR(S): Asahara, Hiroshi; Santoso, Buyung; Guzman, Ernesto; Du, Keyong; **Cole, Philip A.**; Davidson, Irwin; Montminy, Marc
CORPORATE SOURCE: Peptide Biology Laboratories, Salk Institute for Biological Studies, La Jolla, CA, 92037-1002, USA
SOURCE: Molecular and Cellular Biology (2001), 21(23), 7892-7900
CODEN: MCEBD4; ISSN: 0270-7306
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The cAMP-responsive factor CREB induces target gene expression via

constitutive (Q2) and inducible (KID, for **kinase**-inducible domain) activation domains that function synergistically in response to cellular signals. KID stimulates transcription via a phospho (Ser133)-dependent interaction with the coactivator paralogs CREB binding protein and p300, whereas Q2 recruits the TFIID complex via a direct association with hTAFII 130. Here the authors investigate the mechanism underlying cooperativity between the Q2 domain and KID in CREB by in vitro transcription assay with naked DNA and chromatin templates containing the cAMP-responsive somatostatin promoter. The Q2 domain was highly active on a naked DNA template, and Ser133 phosphorylation had no addnl. effect on transcriptional initiation in crude exts. Q2 activity was repressed on a chromatin template, however, and this repression was relieved by the phospho (Ser133) KID-dependent recruitment of p300 histone acetyltransferase activity to the promoter. In chromatin immunopptn. assays of NIH 3T3 cells, cAMP-dependent recruitment of p300 to the somatostatin promoter stimulated acetylation of histone H4. Correspondingly, overexpression of hTAFII130 potentiated CREB activity in cells exposed to cAMP, but had no effect on reporter gene expression in unstimulated cells. The authors propose that cooperativity between the KID and Q2 domains proceeds via a chromatin-dependent mechanism in which recruitment of p300 facilitates subsequent interaction of CREB with TFIID.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 33 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:832382 HCAPLUS
DOCUMENT NUMBER: 136:114346
TITLE: Site-specific incorporation of a phosphotyrosine mimetic reveals a role for tyrosine phosphorylation of SHP-2 in cell signaling
AUTHOR(S): Lu, Wei; Gong, Delquin; Bar-Sagi, Dafna; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Molecular Cell (2001), 8(4), 759-769
CODEN: MOCEFL; ISSN: 1097-2765
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The regulation of protein tyrosine phosphatase (PTPase) SHP-2 is proposed to involve tyrosine phosphorylation on two tail tyrosine residues. Using "expressed protein ligation", nonhydrolyzable phosphotyrosine analogs were introduced at known phosphorylation sites in SHP-2. Biochem. anal. suggests that a phosphonate at Tyr542 interacts intramolecularly with the N-terminal SH2 domain to relieve basal inhibition of the PTPase, whereas a phosphonate at Tyr-580 stimulates the PTPase activity by interaction with the C-terminal SH2 domain. Microinjection expts. indicate that a single phosphorylation of Tyr-542 of SHP-2 is sufficient to activate the MAP **kinase** pathway in living cells. These studies support a novel mechanism explaining how tyrosine phosphorylation of a PTPase is important in signal transduction.

REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 34 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:678637 HCAPLUS
DOCUMENT NUMBER: 136:2189
TITLE: Transcriptional coactivator protein p300. Kinetic characterization of its histone acetyltransferase

activity
AUTHOR(S): Thompson, Paul R.; Kurooka, Hisanori; Nakatani, Yoshihiro; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, The Johns Hopkins University, Baltimore, MD, 21205, USA
SOURCE: Journal of Biological Chemistry (2001), 276(36), 33721-33729
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The p300/cAMP response element-binding protein-binding protein (CBP) family members include human p300 and cAMP response element-binding protein-binding protein, which are both important transcriptional coactivators and histone acetyltransferases. Although the role of these enzymes in transcriptional regulation has been extensively documented, the mol. mechanisms of p300 and CBP histone acetyltransferase catalysis are poorly understood. Herein, the authors describe the first detailed kinetic characterization of p300 using full-length purified recombinant enzyme. These studies have employed peptide substrates to systematically examine the substrate specificity requirements and the kinetic mechanism of this enzyme. The importance of nearby pos. charged residues in lysine targeting was demonstrated. The strict structural requirement of the lysine side chain was shown. The catalytic mechanism of p300 was shown to follow a ping-pong kinetic pathway and viscosity expts. revealed that product release and/or a conformational change were likely rate-limiting in catalysis. Detailed anal. of the p300 selective **inhibitor** Lys-CoA the results showed that it exhibited slow, tight-binding kinetics.
REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 35 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:637152 HCAPLUS
TITLE: Chemical approaches to tyrosine phosphorylation
AUTHOR(S): **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University, Baltimore, MD, 21205, USA
SOURCE: Abstracts of Papers, 222nd ACS National Meeting, Chicago, IL, United States, August 26-30, 2001 (2001), BIOL-141. American Chemical Society: Washington, D. C.
CODEN: 69BUZP
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Protein tyrosine **kinases** catalyze the transfer of a phosphoryl group from ATP to the tyrosine side chains of proteins and play important roles in signal transduction. We will report on our progress to apply a variety of chemical synthesis and kinetic methods to elucidate the structure, function, and regulation of tyrosine **kinases** and the substrates that they phosphorylate. Relevance of our findings to cell signalling and/or drug design will be discussed.

L7 ANSWER 36 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:604186 HCAPLUS
DOCUMENT NUMBER: 135:315182
TITLE: Protein Tyrosine **Kinase** Csk-Catalyzed Phosphorylation of Src Containing Unnatural Tyrosine Analogues
AUTHOR(S): Wang, Dongxia; **Cole, Philip A.**

CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Journal of the American Chemical Society (2001), 123(37), 8883-8886
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Using expressed protein ligation, five unnatural tyrosine analogs (amino-phenylalanine, homotyrosine, 2-methyl-tyrosine, (αS,βR)-β-methyl-tyrosine, and 2,6-difluoro-tyrosine) were incorporated into Src in place of the natural tail tyrosine residue. These semisynthetic substrates were evaluated as Csk substrates or allosteric activators. It appears that the tyrosine phenol hydroxyl is unlikely to be contributing significantly to Src's ground-state binding affinity for Csk. It has been observed that stabilizing tyrosine conformers can further optimize Src's already high substrate efficiency. These latter findings contrast similar studies with synthetic peptide substrates and highlight the value of investigation of protein **kinase** substrate selectivity with protein substrates.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 37 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:561080 HCAPLUS
DOCUMENT NUMBER: 135:192000
TITLE: Probing the mechanism of enzymatic phosphoryl transfer with a chemical trick
AUTHOR(S): Thompson, Paul R.; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University, Baltimore, MD, 21205, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2001), 98(15), 8170-8171
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 25 refs. and commentary on the research of Cho et al. (PNAS 2001, 98, 8525-8530). Nucleophilic substitutions at phosphorus comprise one of the most important classes of reactions in biol. Phosphate diester substitution reactions are catalyzed by nucleases and polymerases and are critical in DNA replication and transcription. Phosphate monoester (phosphoryl transfer) reactions are catalyzed by GTPases, ATPases, protein and small mol. **kinases**, and protein and small mol. phosphatases. These enzymes play diverse roles in energy regulation, cell signaling, ion and small mol. transport, and nucleotide synthesis. There have been intensive efforts to try to understand the details of phosphoryl transfer reactions extending from nonenzymic (or enzyme model) systems to the mechanisms of the enzymic reactions, as exemplified by the study by Cho et al. in the current issue of PNAS. Cho et al. have determined the crystal structure of phosphoserine phosphatase (PSP) bound to BeF3-; and compared it to the structure of a related protein CheY, also bound to BeF3-. The paper by Cho et al. underscores the utility of studying smaller, less complicated proteins as tools to gain insights into the mol. mechanisms of larger, structurally related proteins that may be multidomain, highly regulated or difficult to obtain in sufficient quantities for biochem. studies.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 38 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:457578 HCAPLUS
DOCUMENT NUMBER: 135:189742
TITLE: **Bisubstrate** Ketone Analogues as Serotonin N-Acetyltransferase **Inhibitors**
AUTHOR(S): Kim, Cheol Min; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Journal of Medicinal Chemistry (2001), 44(15), 2479-2485
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Serotonin N-acetyltransferase, also called the melatonin rhythm enzyme, is thought to play an important regulatory role in circadian rhythm in animals and people. A series of analogs were synthesized in which indole and CoA were linked via ketone tethers as designed **inhibitors** of this enzyme. These compds. were tested against purified serotonin N-acetyltransferase. The parent ketone compound was as potent as an amide linked compound studied previously, suggesting that there are no key hydrogen bonds to the nitrogen atom of the corresponding substrate necessary for tight inhibition. Reduction of the parent ketone afforded the diastereomeric carbinol mixture which showed reduced inhibitory potency, arguing against tetrahedral analog mimicry as an important inhibitory theme. Several conformationally constrained ketone analogs were synthesized and investigated, and the results indicated that directing the orientation of the two substrates within the **bisubstrate** system could be used to maximize enzyme inhibition.
REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 39 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:362203 HCAPLUS
DOCUMENT NUMBER: 135:73233
TITLE: Mechanistic studies on the alkyltransferase activity of serotonin N-acetyltransferase
AUTHOR(S): Zheng, Weiping; Scheibner, Kara A.; Ho, Anthony K.; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Chemistry & Biology (2001), 8(4), 379-389
CODEN: CBOLE2; ISSN: 1074-5521
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:73233
AB Background: Serotonin N-acetyltransferase (arylalkylamine N-acetyltransferase, AANAT) catalyzes the first, rate-limiting step in the biosynthesis of the circadian hormone melatonin (5-methoxy-N-acetyltryptamine) from serotonin. Our recent discovery that, in addition to catalyzing the acetyl transfer from acetyl-CoA (acetyl-CoASH) to serotonin, AANAT is also a robust catalyst for the alkyl transfer reaction between CoASH and N-bromoacetyltryptamine has not only opened up a new way to develop cell-permeable AANAT acetyltransferase **inhibitors** that are valuable in vivo tools in helping elucidate melatonin's (patho)physiol. roles, but has also raised a question - how does AANAT

accelerate the alkyl transfer reaction. In this study, mechanistic aspects of the AANAT-catalyzed alkyl transfer reaction were explored by employing CoASH and a series of N-haloacetyltryptamines that were also evaluated for their AANAT acetyltransferase inhibitory activities. Results: Investigation of various N-haloacetyltryptamine analogs showed a similar leaving group effect on the enzymic and non-enzymic reaction rates. Steady-state kinetic analyses demonstrated that AANAT alkyltransferase obeys a sequential, ternary complex mechanism, with random substrate binding. Rate vs. pH profiles revealed the catalytic importance of an ionizable group with pKa .apprx. 7. All those N-haloacetyltryptamines that serve as substrates of AANAT alkyltransferase are also potent (low micromolar) in vitro **inhibitors** against AANAT acetyltransferase activity. In particular, N-chloroacetyltryptamine was also shown to be a potent **inhibitor** of intracellular melatonin production in a pineal cell culture assay. Conclusions: This is the first detailed investigation of the alkyltransferase activity associated with an acetyltransferase. Our results indicate that AANAT does not accelerate the alkyl transfer reaction by simple approximation effect as previously proposed for the similar alkyl transfer reaction catalyzed by other acyltransferases. This study has general implications for developing novel **inhibitors** by taking advantage of the promiscuous alkyltransferase activity associated with several acyltransferases.

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 40 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:334042 HCAPLUS
DOCUMENT NUMBER: 135:118539
TITLE: **Kinase** chips hit the proteomics era
AUTHOR(S): Williams, D. M.; **Cole, P. A.**
CORPORATE SOURCE: Dept of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Trends in Biochemical Sciences (2001), 26(5), 271-273
CODEN: TBSCDB; ISSN: 0376-5067
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB The title research of Zhu, H. et al (Nat. Genet. 26, pg. 283-289, 2000) is reviewed with commentary and 15 refs. Protein **kinase** chips, in which **kinases** are tested for their ability to phosphorylate immobilized substrates, have been developed and used to evaluate the protein **kinases** encoded by the yeast genome. This new technol. promises to be a valuable addition to the biochemists' and cell biologists' arsenal for evaluating the substrate selectivity and function of protein **kinases** in cell signaling.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 41 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:44827 HCAPLUS
DOCUMENT NUMBER: 134:233500
TITLE: Molecular Determinants for Csk-Catalyzed Tyrosine Phosphorylation of the Src Tail
AUTHOR(S): Wang, Dongxia; Huang, Xin-Yun; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Biochemistry (2001), 40(7), 2004-2010
CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Phosphorylation of a critical tail tyrosine residue in Src modulates its three-dimensional structure and protein tyrosine **kinase** activity. The protein tyrosine **kinase** Csk is responsible for catalyzing the phosphorylation of this key Src tyrosine residue, but the detailed mol. basis for Src recognition and catalysis is poorly understood. In this study, we investigate this phosphorylation event using purified recombinant Csk and Src proteins and mutants. It was shown that the apparent kcat and Km values for Csk phosphorylation of catalytically impaired Src (dSrc) are similar to the parameters for Csk-catalyzed phosphorylation of the Src family member Lck. The SH3 (Src homol. 3) and SH2 (Src homol. 2) domains of dSrc were fully dispensable with respect to rapid phosphorylation, indicating that the catalytic domain and tail of dSrc are sufficient for the high efficiency of dSrc as a substrate. Of the eight Src tail residues examined, only the fully conserved Glu (Y-3 position) and Gln (Y-1 position) investigated by alanine scanning mutagenesis caused large redns. (10-40-fold) in dSrc substrate efficiency. The Y-3 Glu requirement was stringent as conservative replacements with Asp or Gln were no better than Ala whereas replacement of the Y-1 Gln with Ile was readily tolerated. Interestingly, en bloc replacement of the tail with a seven amino acid consensus sequence derived from a peptide library anal. was no better than the wild-type sequence. Surprisingly, the dSrc Y527F protein, although not a Csk substrate, enhanced Csk-catalyzed phosphorylation of dSrc. These results and other data suggest that Src dimerization (or higher order oligomerization) is important for high-efficiency Csk-catalyzed phosphorylation of the Src tail.
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 42 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:878500 HCAPLUS
DOCUMENT NUMBER: 134:204291
TITLE: Chemical rescue of a mutant protein-tyrosine **kinase**
AUTHOR(S): Williams, Daniel M.; Wang, Dongxia; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Journal of Biological Chemistry (2000), 275(49), 38127-38130
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Protein-tyrosine **kinases** contain a catalytic loop Arg residue located either two or four positions downstream of a highly conserved Asp residue. In this study, the role of this Arg (Arg-318) in the protein-tyrosine **kinase** C-terminal Src **kinase** (Csk) was investigated. The observed kcat for phosphorylation of the random copolymer poly(Glu,Tyr) substrate by Csk R318A is .apprx.3000-fold smaller compared with that of wild type Csk, whereas the Km values for ATP and poly(Glu,Tyr) are only mildly affected. The kcat value for poly(Glu,Tyr) phosphorylation by the Csk double mutant A316R,R318A is 100-fold greater than the kcat value for the single R318A mutant, suggesting that an Arg positioned at the alternative location fulfills a similar function as in

wild type. Csk R318A **kinase** activity can also be partially recovered by several exogenous small mols. including guanidinium and imidazole. These mols. contain key features whose roles in catalysis can be rationalized from a known x-ray structure of the insulin receptor tyrosine **kinase.** Imidazole is the best of these activators, enhancing phosphorylation rates by Csk R318A up to 100-fold for poly(Glu,Tyr) and significantly stimulating Csk R318A phosphorylation of the physiol. substrate Src. This chemical rescue of mutant protein **kinase** activity might find applications in cell signal transduction expts.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 43 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:241819 HCAPLUS
DOCUMENT NUMBER: 133:70560
TITLE: HATs off: selective synthetic **inhibitors** of the histone acetyltransferases p300 and PCAF
AUTHOR(S): Lau, Ontario D.; Kundu, Tapas K.; Soccio, Raymond E.; Ait-Si-Ali, Slimane; Khalil, Ehab M.; Vassilev, Alex; Wolffe, Alan P.; Nakatani, Yoshihiro; Roeder, Robert G.; **Cole, Philip A.**
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Molecular Cell (2000), 5(3), 589-595
CODEN: MOCEFL; ISSN: 1097-2765
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Histone acetyltransferases (HATs) play important roles in the regulation of gene expression. In this report, we describe the design, synthesis, and application of peptide CoA conjugates as selective HAT **inhibitors** for the transcriptional coactivators p300 and PCAF. Two **inhibitors** (Lys-CoA for p300 and H3-CoA-20 for PCAF) were found to be potent (IC50 $\approx$ 0.5 μM) and selective (.apprx.200-fold) in blocking p300 and PCAF HAT activities. These **inhibitors** were used to probe enzymic and transcriptional features of HAT function in several assay systems. These compds. should be broadly useful as biol. tools for evaluating the roles of HATs in transcriptional studies and may serve as lead agents for the development of novel antineoplastic therapeutics.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 44 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2000:84845 HCAPLUS
DOCUMENT NUMBER: 132:121541
TITLE: Crystal structure of a Ras-Sos complex and its use in rational drug design
INVENTOR(S): Boriack-Sjodin, Ann; Margarit, S. Mariana; Bar-Sagi, Dafna; **Cole, Philip**; Kuriyan, John
PATENT ASSIGNEE(S): The Rockefeller University, USA
SOURCE: PCT Int. Appl., 224 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000005258	A1	20000203	WO 1999-US16348	19990720
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6156526	A	20001205	US 1998-119794	19980721
AU 9953179	A1	20000214	AU 1999-53179	19990720
PRIORITY APPLN. INFO.:			US 1998-119794	A2 19980721
			WO 1999-US16348	W 19990720

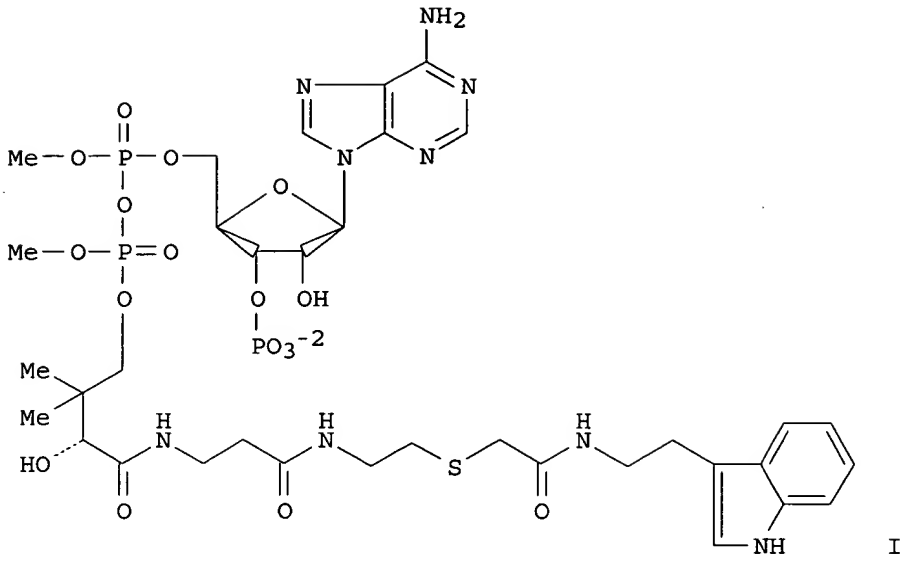
AB A detailed 3-dimensional structure for the complex formed between Ras and the Son of sevenless (Sos) protein is provided. Specifically, x-ray crystallog. data are provided for the complex of a C-terminally truncated form of human H-Ras (residues 1-166) with the guanine nucleotide-exchange factor region of human Sos1 (residues 564-1049). The crystals of this complex have a space group of I422 and unit cell dimensions of a = 142.7 Å, b = 142.7 Å, and c = 207.9 Å. The structure reveals that Sos interacts extensively with Ras and stabilizes it in a nucleotide-free state by displacing the residues that coordinate the magnesium ion and the phosphate groups of the nucleotide and by partially occluding the magnesium binding site. The structure also suggests a pathway for the rebinding of nucleotides to Ras, with consequent release of Sos, a process that is crucial for the functioning of Sos as a nucleotide exchanger rather than a binding **inhibitor.** The interaction between these 2 proteins plays a key role in the regulation of cell proliferation, and the present invention therefore provides procedures for identifying agents that can inhibit tumor proliferation through the use of rational drug design predicated on the crystals and crystallog. data disclosed.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 45 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:748305 HCAPLUS
DOCUMENT NUMBER: 132:456
TITLE: **Inhibitors** of serotonin N-acetyltransferase
INVENTOR(S): **Cole, Philip A.**; Khalil, Ehab
PATENT ASSIGNEE(S): The Rockefeller University, USA
SOURCE: U.S., 40 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5990094	A	19991123	US 1998-14340	19980127
PRIORITY APPLN. INFO.:			US 1998-14340	19980127

GI



I

AB Compds. and pharmaceutical compns. which inhibit serotonin N-acetyltransferase enzyme and modulate the serotonin-melatonin pathway are described. Potent **inhibitors** of serotonin N-acetyltransferase serve as biol. tools that help reveal biol. functions for melatonin and pineal serotonin in vivo. Ultimately, they can even serve as therapeutic agents for a variety of different conditions, perhaps by allowing pineal serotonin and melatonin to be artificially regulated. A synthetic **bisubstrate** compound (I), which incorporated the indole and CoA moieties of the two substrates (acetyl-CoA and tryptamine), was an extremely potent serotonin N-acetyltransferase **inhibitor**, the IC50 of 150 mM being near the expected range to be effective for in vivo studies.

REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 46 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:728878 HCAPLUS
DOCUMENT NUMBER: 132:44826
TITLE: Mechanism-based inhibition of the melatonin rhythm enzyme: pharmacologic exploitation of active site functional plasticity
AUTHOR(S): Khalil, Ehab M.; De Angelis, Jacqueline; Ishii, Makoto; **Cole, Philip A.**
CORPORATE SOURCE: Laboratory of Bioorganic Chemistry, The Rockefeller University, New York, NY, 10021, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1999), 96(22), 12418-12423
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Serotonin N-acetyltransferase is the enzyme responsible for the diurnal rhythm of melatonin production in the pineal gland of animals and humans. **Inhibitors** of this enzyme active in cell culture have not been reported previously. The compound N-bromoacetyltryptamine was shown to be a potent **inhibitor** of this enzyme in vitro and in a pineal cell

culture assay (IC50 ≈ 500 nM). The mechanism of inhibition is suggested to involve a serotonin N-acetyltransferase-catalyzed alkylation reaction between N-bromoacetyltryptamine and reduced CoA, resulting in the production of a tight-binding **bisubstrate** analog **inhibitor** . This alkyltransferase activity is apparently catalyzed at a functionally distinct site compared with the acetyltransferase activity active site on serotonin N-acetyltransferase. Such active site plasticity is suggested to result from a subtle conformational alteration in the protein. This plasticity allows for an unusual form of mechanism-based inhibition with multiple turnovers, resulting in "mol. fratricide.". N-bromoacetyltryptamine should serve as a useful tool for dissecting the role of melatonin in circadian rhythm as well as a potential lead compound for therapeutic use in mood and sleep disorders.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 47 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:474360 HCAPLUS
DOCUMENT NUMBER: 131:254182
TITLE: Domain interactions in protein tyrosine **kinase** Csk
AUTHOR(S): Sondhi, Dolan; **Cole, Philip A.**
CORPORATE SOURCE: Laboratory of Bioorganic Chemistry, The Rockefeller University, New York, NY, 10021, USA
SOURCE: Biochemistry (1999), 38(34), 11147-11155
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Csk (C-terminal Src **kinase**) is a protein tyrosine **kinase** that phosphorylates Src family member C-terminal tails, resulting in down-regulation of Src family members. It is composed of three principal domains: an SH3 (Src homol. 3) domain, an SH2 (Src homol. 2) domain, and a catalytic domain. The impact of the noncatalytic domains on **kinase** catalysis was investigated. The Csk catalytic domain was expressed in Escherichia coli as a recombinant glutathione S-transferase-fusion protein and demonstrated to have 100-fold reduced catalytic efficiency. Production of the catalytic domain by proteolysis of full-length Csk afforded a similar rate reduction This suggested that the reduction in catalytic efficiency of the recombinant catalytic domain was intrinsic to the sequence and not an artifact related to faulty expression. This rate reduction was similar for peptide and protein substrates and was due almost entirely to a reduced kcat rather than to effects on substrate Kms. Viscosity expts. on the catalytic fragment **kinase** reaction demonstrated that the chemical (phosphoryl transfer) step had a reduced rate. While the Csk SH2 domain had no intermol. effect on the **kinase** activity of the Csk catalytic domain, the SH3 domain and SH3-SH2 fragment led to a partial rescue (4-5-fold) of the lost **kinase** activity. This rescue was not achieved with two other SH3 domains (lymphoid cell **kinase**, Abelson **kinase**). The extrapolated Kd of interaction for the Csk catalytic domain with the Csk SH3 domain was 2.2 μM and that of the Csk catalytic domain with the Csk SH3-SH2 fragment was 8.8 μM. Taken together, these findings suggest that there is likely an intramol. interaction between the catalytic and SH3 domains in full-length Csk that is important for efficient catalysis. By employing a Csk SH3 specific type II polyproline helix peptide and carrying out site-directed mutagenesis, it was established that the SH3 surface that interacts with the catalytic domain was distinct from the surface that binds type II polyproline helix peptides. This finding suggests a novel mode of protein-protein interaction for an SH3 domain.

The implications for Csk substrate selectivity, regulation, and function are discussed.

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 48 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:397260 HCAPLUS
DOCUMENT NUMBER: 131:196270
TITLE: Chemical approaches to the study of protein tyrosine **kinases** and their implications for mechanism and **inhibitor** design
AUTHOR(S): **Cole, Philip A.**; Sondhi, Dolan; Kim, Kyonghee
CORPORATE SOURCE: Laboratory of Bioorganic Chemistry, The Rockefeller University, New York, NY, 10021, USA
SOURCE: Pharmacology & Therapeutics (1999), 82(2-3), 219-229
CODEN: PHTHDT; ISSN: 0163-7258
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Protein tyrosine **kinases** are critical enzymes for signal transduction. Using C-terminal Src **kinase** (Csk) as a model system, we discuss progress in three main areas. First, we describe our efforts to measure the transition state of the reaction using peptide substrates containing fluorotyrosine analogs. It is shown that the Bronsted nucleophile coefficient for the reaction is near zero (similar to the nonenzymic reaction) and the required nucleophile is the neutral phenol (rather than the more chemical reactive phenoxide anion). By studying the **kinase** reaction in the reverse direction, a Bronsted leaving group coefficient of -0.3 was measured, indicative of protonation of the departing phenol in the transition state. Taken together, these results strongly support a dissociative transition state mechanism for the **kinase** . These findings set constraints on the design of transition state analog **inhibitors.** Second, we describe efforts toward defining the specificity of Csk for peptide and protein substrates. The main findings are that local amino acids surrounding a phosphorylated tyrosine can influence recognition, but that long-range interactions probably are more important in a physiol. protein substrate. These findings underscore the complexities in how protein **kinases** select protein substrates. Third, we describe a new method in protein engineering that has been applied to the study of protein **kinases.** The method, expressed protein ligation, allows a general approach for ligating synthetic peptides to recombinant proteins. Using expressed protein ligation, obtaining site-specifically phosphorylated proteins and proteins with the incorporation of biophys. probes becomes relatively straightforward. We have used this method to generate a tail phosphorylated, conformationally altered Csk that showed an unexpected increase in **kinase** activity.

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 49 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:306632 HCAPLUS
DOCUMENT NUMBER: 131:73935
TITLE: Synthesis of (2S,3R)-β-methyltyrosine catalyzed by tyrosine phenol-lyase
AUTHOR(S): Kim, Kyonghee; **Cole, Philip A.**
CORPORATE SOURCE: Laboratory of Bioorganic Chemistry, Rockefeller University, New York, NY, 10021, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1999), 9(8),

1205-1208
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 131:73935
AB A one-step enzymic synthesis of the conformationally restrained tyrosine analog (2S,3R)-β-methyltyrosine is reported. This synthesis extends the preparative chemical associated with tyrosine phenol-lyase. The β-methyltyrosine derivative was shown to be an efficient protein tyrosine **kinase** substrate, suggesting that conformational restraint may ultimately be used to enhance tyrosine **kinase** recognition of substrates.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 50 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:748871 HCAPLUS
DOCUMENT NUMBER: 130:106804
TITLE: Indoleamine analogs as probes of the substrate selectivity and catalytic mechanism of serotonin N-acetyltransferase
AUTHOR(S): Khalil, Ehab M.; De Angelis, Jacqueline; **Cole, Philip A.**
CORPORATE SOURCE: Laboratory of Bioorganic Chemistry, Rockefeller University, New York, NY, 10021, USA
SOURCE: Journal of Biological Chemistry (1998), 273(46), 30321-30327
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Serotonin N-acetyltransferase (arylalkylamine N-acetyltransferase (AANAT)) catalyzes the reaction of serotonin (or tryptamine) with acetyl-CoA to form N-acetylserotonin (or N-acetyltryptamine) and is responsible for the melatonin circadian rhythm in vertebrates. This study evaluates a series of indoleamine analogs as alternate substrates of AANAT. 3-Indolepropylamine and 3-indolebutylamine were chemical synthesized and found to be processed by AANAT, although 20- and 60-fold less efficiently compared with the natural substrate serotonin, resp. Racemic α-methyltryptamine and Nω-methyltryptamine were also shown to be substrates for AANAT, again with reduced kcat and kcat/Km compared with serotonin. The enzyme did exhibit .apprx.9:1 stereoselectivity for the R-enantiomer of α-methyltryptamine vs. the S-enantiomer. By measuring the enzymic rates vs. increasing buffer microviscosity, it was demonstrated that diffusional release of product is most likely the principal rate-determining step for the enzymic transformation of tryptamine (which has similar kcat and kcat/Km compared with serotonin). Anal. of kcat and kcat/Km vs. pH for the poor substrate Nω-methyltryptamine showed that an ionizable group on the enzyme with pKa .apprx. 7, required to be in its deprotonated form, may be important in catalysis. The α-methyltryptamine analog α-trifluoromethyltryptamine was not processed by the enzyme, but served as a modest competitive **inhibitor.** Taken together with the pH-rate anal., these results favor a model in which the serotonin substrate binds to the enzyme as the pos. charged ammonium salt, and nucleophilicity of the amine is important in enzyme-catalyzed acetyl transfer.
REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 51 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:431209 HCAPLUS
DOCUMENT NUMBER: 129:172344
TITLE: Kinetic analysis of a protein tyrosine **kinase** reaction transition state in the forward and reverse directions
AUTHOR(S): Kim, Kyonghee; **Cole, Philip A.**
CORPORATE SOURCE: Laboratory of Bioorganic Chemistry, Rockefeller University, New York, NY, 10021, USA
SOURCE: Journal of the American Chemical Society (1998), 120(28), 6851-6858
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Protein tyrosine **kinases** catalyze the transfer of the γ-phosphoryl group from ATP to tyrosine residues in proteins and are important enzymes in cell signal transduction. We have investigated the catalytic phosphoryl transfer transition state of a protein tyrosine **kinase** reaction catalyzed by Csk by analyzing a series of fluorotyrosine-containing peptide substrates. It was established for five such fluorotyrosine-containing peptide substrates that there is good agreement between the tyrosine analog phenol pKa and the ionizable group responsible for the basic limb of a pH rate profile anal. This indicates that the substrate tyrosine phenol must be neutral to be enzymically active. Taken together with previous data indicating a small βnucleophile coefficient (0-0.1), these results strongly support a dissociative transition state for phosphoryl transfer. In addition, the βleaving group coefficient was measured for the reverse protein tyrosine **kinase** reaction and shown to be -0.3. This value is in good agreement with a previously reported nonenzymic model phosphoryl transfer reaction carried out under acidic conditions (pH 4) and is most readily explained by a transition state with significant proton transfer to the departing phenol.
REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 52 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:378466 HCAPLUS
DOCUMENT NUMBER: 129:118455
TITLE: Expressed protein ligation: A general method for protein engineering
AUTHOR(S): Muir, Tom W.; Sondhi, Dolan; **Cole, Philip A.**
CORPORATE SOURCE: Laboratory of Synthetic Protein Chemistry, Rockefeller University, New York, NY, 10021, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1998), 95(12), 6705-6710
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A protein semisynthesis method-expressed protein ligation-is described that involves the chemoselective addition of a peptide to a recombinant protein. This method was used to ligate a phosphotyrosine peptide to the C terminus of the protein tyrosine **kinase** C-terminal Src **kinase** (Csk). By intercepting a thioester generated in the recombinant protein with an N-terminal cysteine containing synthetic peptide, near quant. chemical ligation of the peptide to the protein was achieved. The semisynthetic tail-phosphorylated Csk showed evidence of an intramol. phosphotyrosine-Src homol. 2 interaction and an unexpected increase in

catalytic phosphoryl transfer efficiency toward a physiol. relevant substrate compared with the non-tail-phosphorylated control. This work illustrates that expressed protein ligation is a simple and powerful new method in protein engineering to introduce sequences of unnatural amino acids, posttranslational modifications, and biophys. probes into proteins of any size.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 53 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:373235 HCAPLUS
DOCUMENT NUMBER: 129:132919
TITLE: A Potent **Inhibitor** of the Melatonin Rhythm Enzyme
AUTHOR(S): Khalil, Ehab M.; **Cole, Philip A.**
CORPORATE SOURCE: Laboratory of Bioorganic Chemistry, Rockefeller University, New York, NY, 10021, USA
SOURCE: Journal of the American Chemical Society (1998), 120(24), 6195-6196
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Inhibitors** of melatonin biosynthesis could not only help improve our understanding of circadian rhythm but they might also have therapeutic roles in mood and sleep disorders. The key enzyme to be targeted in this regard is serotonin N-acetyltransferase (arylalkylamine N-acetyltransferase, AANAT), also called the melatonin rhythm enzyme. This paper reports the synthesis and activity of the first potent and specific **inhibitor** of AANAT. This **inhibitor** is a **bisubstrate** analog which contains covalently linked components of serotonin and acetyl-CoA.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 54 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1998:79094 HCAPLUS
DOCUMENT NUMBER: 128:241144
TITLE: Kinetic analysis of the catalytic mechanism of serotonin N-acetyltransferase (EC 2.3.1.87)
AUTHOR(S): De Angelis, Jacqueline; Gastel, Jonathan; Klein, David C.; **Cole, Philip A.**
CORPORATE SOURCE: Laboratory of Bioorganic Chemistry, The Rockefeller University, New York, NY, 10021, USA
SOURCE: Journal of Biological Chemistry (1998), 273(5), 3045-3050
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Serotonin N-acetyltransferase (arylalkylamine N-acetyltransferase, AANAT, EC 2.3.1.87) is the penultimate enzyme in melatonin biosynthesis. This enzyme is of special biol. interest because large changes in its activity drive the large night/day rhythm in circulating melatonin in vertebrates. In this study, the kinetic mechanism of AANAT action was studied using a bacterially expressed glutathione S-transferase (GST)-AANAT fusion protein. The enzymol. behaviors of GST-AANAT and cleaved AANAT were essentially identical. Two-substrate kinetic anal. generated an intersecting line pattern characteristic of a ternary complex mechanism.

The dead end **inhibitor** analog desulfo-CoA was competitive vs. acetyl-CoA and noncompetitive vs. tryptamine. Tryptophol was not an alternative substrate but was a dead end competitive **inhibitor** vs. tryptamine and an uncompetitive **inhibitor** vs. acetyl-CoA, indicative of an ordered binding mechanism requiring binding of acetyl-CoA first. N-Acetyl-tryptamine, a reaction product, was a noncompetitive **inhibitor** vs. tryptamine and uncompetitive with respect to acetyl-CoA. Taken together, these results support an ordered BiBi ternary complex (sequential) kinetic mechanism for AANAT and provide a framework for **inhibitor** design.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 55 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:794353 HCAPLUS
DOCUMENT NUMBER: 128:125196
TITLE: Peptide and Protein Phosphorylation by Protein Tyrosine **Kinase** Csk: Insights into Specificity and Mechanism
AUTHOR(S): Sondhi, Dolan; Xu, Wenqing; Songyang, Zhou; Eck, Michael J.; **Cole, Philip A.**
CORPORATE SOURCE: Laboratory of Bioorganic Chemistry, Rockefeller University, New York, NY, 10021, USA
SOURCE: Biochemistry (1998), 37(1), 165-172
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Csk (C-terminal Src **kinase**) is a protein tyrosine **kinase** that phosphorylates Src family member C-terminal tails, resulting in down-regulation of Src family members. The mol. basis of Csk's substrate specificity and catalytic mechanism with a protein substrate was investigated. Using a peptide library approach, preferential amino acids which are unrelated to the conserved Src C-terminal sequence were identified. The validity of these preferences was confirmed by synthesizing a short consensus peptide and demonstrating its high catalytic efficiency with Csk. These results underscore the difficulties of relying on amino acids neighboring tyrosine in protein sequences as predictors of protein **kinase** substrate specificity for in vivo anal. In addition, a catalytically inactive version of the Src family member, Lck (lymphoid cell **kinase**), was expressed, purified, and evaluated as a Csk substrate. It was proven to be the most catalytically efficient substrate yet identified for Csk. The high efficiency of purified Csk phosphorylating a pure, unphosphorylated Src family member argues against the importance of an SH2-phosphotyrosine docking interaction or the involvement of extra recruitment proteins in facilitating Csk phosphorylation of Src family members. Kinetic studies revealed that the chemical step is at least partially rate-determining in Csk-mediated phosphoryl transfer to the Lck protein. Other properties including preferences for Mn over Mg, thio effects, and Kms for ATP also correlate fairly well between protein and peptide phosphorylation. The lack of a significant impact of increased salt on the Km for Lck phosphorylation differs from Csk-mediated poly(Glu,Tyr) phosphorylation, and argues against the importance of electrostatic effects in the Csk-Lck binding interaction. The failure of the Lck phosphorylation product (phosphotyrosine-505) to significantly inhibit Csk phosphorylation of Lck is consistent with a catalytic model involving multidomain structural interactions between substrate and enzyme.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 56 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:720443 HCAPLUS
DOCUMENT NUMBER: 127:328275
TITLE: Measurement of a Bronsted Nucleophile Coefficient and Insights into the Transition State for a Protein Tyrosine **Kinase**
AUTHOR(S): Kim, Kyonghee; **Cole, Philip A.**
CORPORATE SOURCE: Laboratory of Bioorganic Chemistry, Rockefeller University, New York, NY, 10021, USA
SOURCE: Journal of the American Chemical Society (1997), 119(45), 11096-11097
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The Bronsted nucleophile coefficient (βnuc), a measure of the role of the nucleophile in the transition state, has never before been determined on an ATP-dependent **kinase.** Here, we measure this value on the protein tyrosine **kinase** Csk-catalyzed phosphorylation of a peptide substrate family. At 0.08 ± 0.06, the βnuc is in good agreement with those of analogous non-enzymic reactions and strongly suggests a transition state with dissociative character. Furthermore, the attacking nucleophile in the enzyme reaction is shown to be the neutral tyrosine phenol, not the phenoxide anion. These findings set conceptual constraints on protein **kinase inhibitor** design and regulation.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 57 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:127316 HCAPLUS
DOCUMENT NUMBER: 126:141322
TITLE: Divalent Ion Effects and Insights into the Catalytic Mechanism of Protein Tyrosine **Kinase** Csk
AUTHOR(S): Grace, Miranda R.; Walsh, Christopher T.; **Cole, Philip A.**
CORPORATE SOURCE: Laboratory of Bio-Organic Chemistry, Rockefeller University, New York, NY, 0021, USA
SOURCE: Biochemistry (1997), 36(7), 1874-1881
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Csk (C-terminal Src **kinase**) is a protein tyrosine **kinase** which catalyzes the transfer of the γ-phosphoryl group of ATP to the tyrosine hydroxyl of proteins in the presence of a divalent ion. Previous work with poly(Glu,Tyr) as the tyrosine-containing substrate and Mn as the divalent ion defined a ternary complex mechanism with ADP product release partially rate-determining [Cole, P. A., et al. (1994) J. Biol. Chemical 269, 30880-30887]. In this current study, ionic strength and divalent ion effects were probed. Increasing ionic strength led to a dramatic rise in the poly(Glu,Tyr) [4:1 poly(glutamate:tyrosine)] Km and had little effect on the ATP Km or kcat in Csk-mediated phosphoryl transfer. This finding allowed the dead-end peptide **inhibitor** EDNEFTA to be characterized as a linear competitive **inhibitor** of poly(Glu,Tyr) and a linear noncompetitive **inhibitor** of ATP. Taken together with previous data, the overall kinetic mechanism could now be assigned as random substrate binding, ternary complex. Compared to Mn, Mg was shown to sustain phosphoryl transfer with a 2.5-fold higher kcat but Km's for

ATP and poly(Glu,Tyr) that were some 15-20-fold higher. An elevated ADP Ki and microviscosity effects were most suggestive of a kinetic mechanism with fast ADP release, and the chemical step fully rate-determining in the Mg-dependent reaction. Steady-state kinetic analyses of Csk reactions with Co and Ni in addition to Mg and Mn on wild-type and D314E Csk with ATP and ATPγS [adenosine 5'-O-(3-thiotriphosphate)] as substrates were performed. The kcat thio effects [kcat(ATP)/kcat(ATPγS)] were inversely correlated with metal thiophilicity in both wild-type and D314E mutant Csk reactions, although the relation was less pronounced in the latter. These results appear to underscore the role of γ-phosphoryl hydrogen bonding/salt bridging in the wild-type Csk reaction transition state, which is somewhat perturbed in the D314E Csk reaction. In the case of the Ni reaction, the kcat thio effect was reduced to about 2 in the wild-type and D314E mutant Csk reactions. Relevance with regard to the degree of nucleophilic attack in the transition state, i.e., associative vs. dissociative character of phosphoryl transfer, is discussed.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 58 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:825203 HCAPLUS
DOCUMENT NUMBER: 123:221576
TITLE: The role of the catalytic base in the protein tyrosine **kinase** Csk
AUTHOR(S): **Cole, Philip A.**; Grace, Miranda R.; Phillips, Robert S.; Burn, Paul; Walsh, Christopher T.
CORPORATE SOURCE: Dep. Biol. Chem. Mol. Pharmacol., Harvard Med. Sch., Boston, MA, 02115, USA
SOURCE: Journal of Biological Chemistry (1995), 270(38), 22105-8
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Bio logy
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A potential distinguishing feature between protein tyrosine **kinases** and homologous serine/threonine **kinases** is the function of the catalytic base in these enzymes. In this study, the authors show that a peptide containing the unnatural amino acid trifluorotyrosine shows remarkably similar efficiency as a substrate of the tyrosine **kinase** Csk (C-terminal Src **kinase**) compared with the corresponding tyrosine-containing peptide despite a 4-unit change in the phenolic pKa. These results argue against the importance of early tyrosine deprotonation by a catalytic base in Csk. To further explore the role of the proposed catalytic base, the Csk mutant protein D314E was produced. This mutant displayed a significant reduction in kcat (approx. 104) but relatively little effect on substrate Km values compared with wild-type Csk. Examination of the thio effect (kcat-ATP/kcat-adenosine 5'-O-(thiotriphosphate)) for D314E Csk led to the suggestion that a role of aspartate 314 may be to enhance the reactivity of the γ-phosphate of ATP toward electrophilic attack. These results may have significant impact on protein tyrosine **kinase inhibitor** design.

L7 ANSWER 59 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:675132 HCAPLUS
DOCUMENT NUMBER: 121:275132
TITLE: Evaluation of the catalytic mechanism of recombinant human Csk (C-terminal Src **kinase**) using nucleotide analogs and viscosity effects
AUTHOR(S): **Cole, Philip A.**; Burn, Paul; Takacs, Bela;

Walsh, Christopher T.
CORPORATE SOURCE: Dep. Biological Chem. Mol. Pharmacol., Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Journal of Biological Chemistry (1994), 269(49), 30880-7
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this study, the authors have investigated the tyrosine **kinase** reaction catalyzed by purified human recombinant Csk (C-terminal Src **kinase**). Poly(Glu,Tyr) 4:1 was used as the tyrosine-containing substrate. Both ATP and poly(Glu,Tyr) were shown to be well behaved saturable substrates for recombinant Csk, with Km values that were in reasonable agreement with literature values reported for the non-recombinant enzyme and with kcat about 40 min-1. A sequential kinetic mechanism is suggested by a steady state kinetic anal. **Inhibitor** studies with ADP and β,γ-imidoadenosine 5'-triphosphate were performed, and these results provided evidence against the possibility that ordered binding of peptide prior to ATP occurs. While a suitable competitive **inhibitor** of poly(Glu,Tyr) has not yet been identified, other evidence pointed to a rapid equilibrium random mechanism. Csk utilized adenosine 5'-O-(3-thiotriphosphate) in place of ATP. The phosphorothioyl transfer occurred with a kcat about 15-20-fold lower than the ATP reaction but with similar Km values. Deuterium solvent isotope effects on kcat were small for both reactions in a pH-independent range, consistent with the possibility that proton transfer is asym. in the reaction transition state. Using viscosity effects, ADP product release was suggested to be partially rate determining for catalysis in the standard ATP
reaction. A comparison of the Csk kinetic mechanism with that of protein **kinase** A is discussed.

L7 ANSWER 60 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:162322 HCAPLUS
DOCUMENT NUMBER: 120:162322
TITLE: Estimates of trace element intakes in Chinese farmers
AUTHOR(S): Chen, Fan; **Cole, Philip**; Wen, Lifang; Mi, Zhibao; Trapido, Edward J.
CORPORATE SOURCE: Sylvester Compr. Cancer Cent., Univ. Miami, Miami, FL, 33136, USA
SOURCE: Journal of Nutrition (1994), 124(2), 196-201
CODEN: JONUAI; ISSN: 0022-3166
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Epidemiol. data on the average daily human dietary intake of the trace elements nickel, cadmium, molybdenum and silicon are scarce worldwide, primarily because foods consumed vary widely over days and seasons. Available full year food allocation records for farmers in rural areas of China provide an unique opportunity to estimate dietary trace elements. In 1988, the authors measured the concns. of zinc, copper, iron, cadmium, nickel, molybdenum, silicon and selenium in different foods by using food samples collected from 232 villages (distributed among 21 communes). These measurements, combined with the food consumption information from existing food allocation records in each commune for an entire year, allowed the authors to estimate the average daily consumption of these trace elements by Chinese farmers. With one exception (an association of zinc and esophageal cancer), the variation of dietary trace elements did not show any association with mortality from several common diseases. The ests. for

some of the dietary trace elements from some subpopulations were either less or more than current recommendations. No increases in mortality were found, however, from diseases normally associated with either dietary deficiencies or excesses of these elements.

L7 ANSWER 61 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:26181 HCAPLUS
DOCUMENT NUMBER: 120:26181
TITLE: Synthetic and enzymic studies with potential alternate substrates for human placental aromatase: 10β-trifluoroacetyl and 10β-allyl steroids
AUTHOR(S): Jaworski, Krysztof; **Cole, Philip A.**; Robinson, Cecil H.
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205-2185, USA
SOURCE: Bioorganic Chemistry (1993), 21(3), 330-41
CODEN: BOCMBM; ISSN: 0045-2068
DOCUMENT TYPE: Journal
LANGUAGE: English
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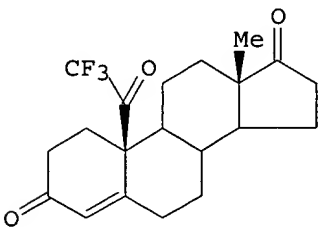

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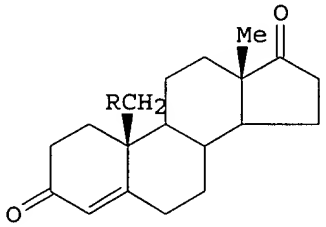

II, R= CH=CH2
III, R=C≡CH

AB The 10β-trifluoroacetyl (I) and 10β-allyl (II) analogs of androstenedione were studied as potential alternate substrates for aromatase. The hitherto undescribed I was prepared via the reaction of trifluoromethyltrimethylsilane with a 19-oxo steroid. There was no conversion of I to estrogen by aromatase, although I was a competitive **inhibitor.** Furthermore II was not epoxidized significantly by the enzyme, leaving open the mechanism of suicide inactivation of aromatase by the propargyl steroid III.

L7 ANSWER 62 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1991:530530 HCAPLUS
DOCUMENT NUMBER: 115:130530
TITLE: A chemical portrait of and **inhibitor** development for cytochrome P-450 aromatase
AUTHOR(S): **Cole, Philip Arthur**
CORPORATE SOURCE: Johns Hopkins Univ., Baltimore, MD, USA
SOURCE: (1991) 359 pp. Avail.: Univ. Microfilms Int., Order No. DA9113651
From: Diss. Abstr. Int. B 1991, 51(12, Pt. 1), 5843
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable

L7 ANSWER 63 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:586943 HCAPLUS
DOCUMENT NUMBER: 113:186943
TITLE: Mechanism and inhibition of cytochrome P-450 aromatase

AUTHOR(S): **Cole, Philip A.**; Robinson, Cecil H.
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Journal of Medicinal Chemistry (1990), 33(11), 2933-42
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with many refs., on the mechanism of the aromatase activity of cytochrome P 450 and its inhibition. Competitive **inhibitors**, suicide inactivators, and affinity labels are examined and future directions for the design of mechanism-based **inhibitors** are discussed.

L7 ANSWER 64 OF 64 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1990:528512 HCAPLUS
DOCUMENT NUMBER: 113:128512
TITLE: Conversion of a 3-desoxysteroid to 3-desoxyestrogen by human placental aromatase
AUTHOR(S): **Cole, Philip A.**; Bean, Joseph M.; Robinson, Cecil H.
CORPORATE SOURCE: Sch. Med., Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1990), 87(8), 2999-3003
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human placental aromatase is a cytochrome P 450 enzyme system which converts androgens to estrogens by 3 successive oxidative reactions. The first 2 steps have been shown to be hydroxylations at the androgen 19-C but the third step remains unknown. A leading theory for the third step involves ferric peroxide attack on the 19-oxo group to produce a 19,19-hydroxyferric peroxide intermediate and subsequent collapse to estrogen. Previously, a nonenzymic peroxide model reaction based on the above-mentioned theory was developed, and the importance of 3-ketone enolization in facilitating aromatization was demonstrated. This study discusses the synthesis and nonenzymic and enzymic study of a 3-desoxy-2,4-diene-19-oxo androgen analog. This compound was a potent nonenzymic model substrate and competitive **inhibitor** of aromatase (Ki = 73 nM). Furthermore, in an unprecedented event, this compound served as a substrate for aromatase, with conversion to the corresponding 3-desoxyestrogen.

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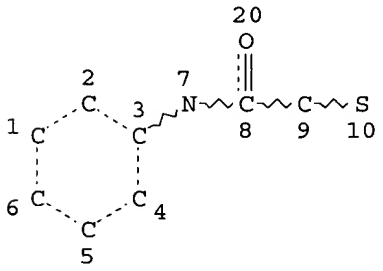

NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 11

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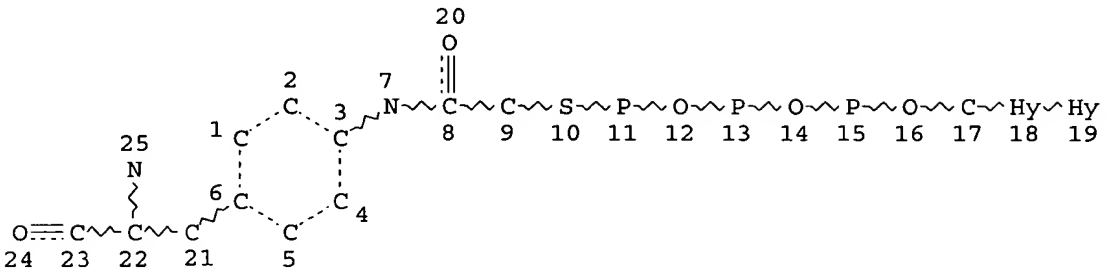
L18 STR



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GGCAT IS PCY AT 19
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE
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L22 4 SEA FILE=HCAPLUS ABB=ON PLU=ON L19

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L22 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:622866 HCAPLUS
DOCUMENT NUMBER: 143:243964
TITLE: Bisubstrate analog probes for the insulin receptor protein tyrosine kinase: Molecular yardsticks for analyzing catalytic mechanism and inhibitor design
AUTHOR(S): Hines, Aliya C.; Parang, Keykavous; Kohanski, Ronald A.; Hubbard, Stevan R.; Cole, Philip A.
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Bioorganic Chemistry (2005), 33(4), 285-297
CODEN: BOCMBM; ISSN: 0045-2068
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Bisubstrate analogs have the potential to provide enhanced specificity for protein kinase inhibition and tools to understand catalytic mechanism. Previous efforts led to the design of a peptide-ATP conjugate bisubstrate analog utilizing aminophenylalanine in place of tyrosine and a thioacetyl

linker to the γ-phosphate of ATP which was a potent inhibitor of the insulin receptor kinase (IRK). In this study, the authors have examined the contributions of various electrostatic and structural elements in the bisubstrate analog to IRK binding affinity. Three types of changes (seven specific analogs in all) were introduced: a Tyr isostere of the previous aminophenylalanine moiety, modifications of the spacer between the adenine and the peptide, and deletions and substitutions within the peptide moiety. These studies allowed a direct evaluation of the hydrogen bond strength between the anilino nitrogen of the bisubstrate analog and the enzyme catalytic base Asp and showed that it contributes 2.5 kcal/mol of binding energy, in good agreement with previous predictions. Modifications of the linker length resulted in weakened inhibitory affinity, consistent with the geometric requirements of an enzyme-catalyzed dissociative transition state. Alterations in the peptide motif generally led to diminished inhibitory potency, and only some of these effects could be rationalized based on prior kinetic and structural studies. Taken together, these results suggest that a combination of mechanism-based design and empirical synthetic manipulation will be necessary in producing optimized protein kinase bisubstrate analog inhibitors.

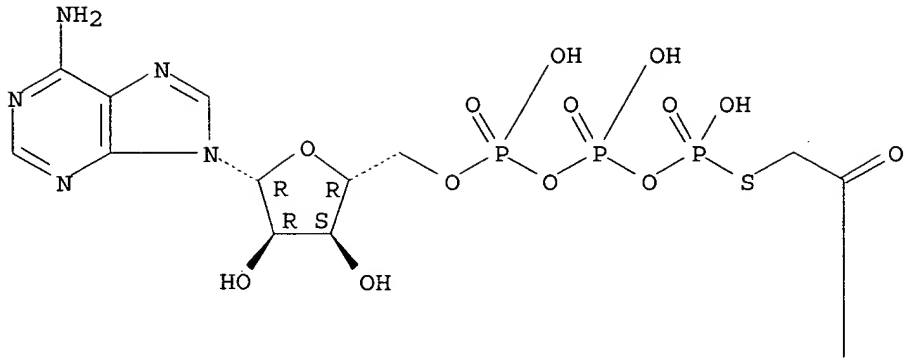
IT **329783-44-0P 863099-24-5P 863099-25-6P**
863099-26-7P 863099-27-8P
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(bisubstrate analog; peptide bisubstrate analog probes preparation and inhibition of insulin receptor protein tyrosine kinase)

RN 329783-44-0 HCAPLUS

CN L-Aspartic acid, N2-acetyl-L-lysyl-L-lysyl-L-lysyl-L-leucyl-L-prolyl-L-alanyl-L-threonylglycyl-L-α-aspartyl-4-[[6-(5'-adenylyloxy)-4,6-dihydroxy-4,6-dioxido-1-oxo-5-oxa-3-thia-4,6-diphosphahex-1-yl]amino]-L-phenylalanyl-L-methionyl-L-asparaginyl-L-methionyl-L-seryl-L-prolyl-L-valylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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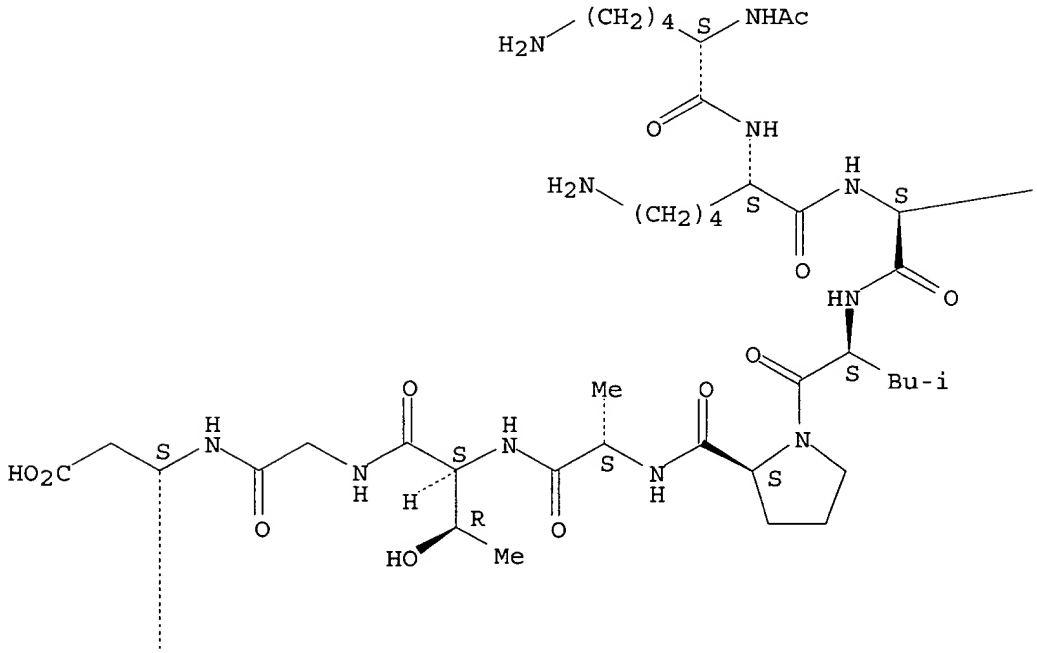

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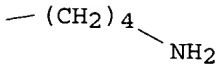

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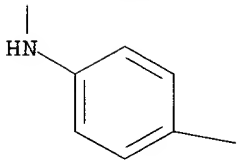

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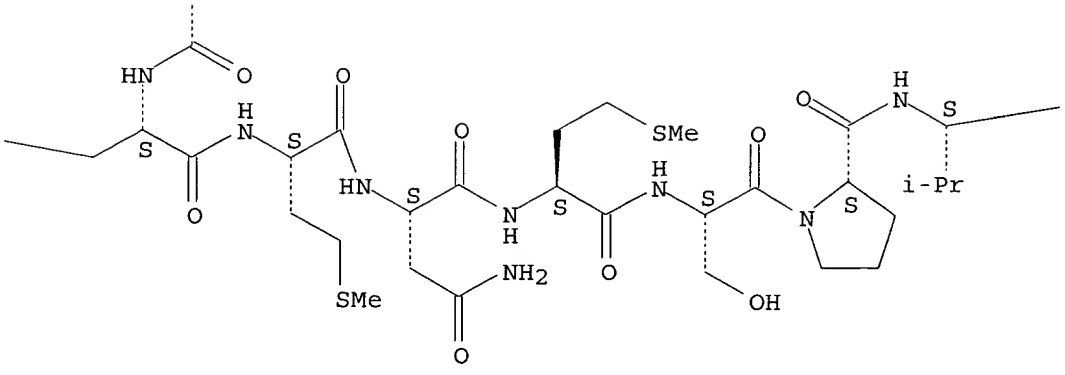

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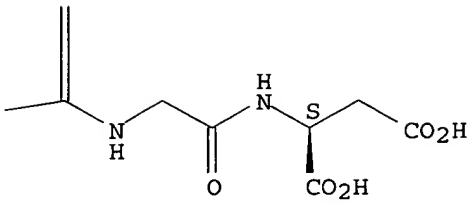

RN 863099-24-5 HCAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

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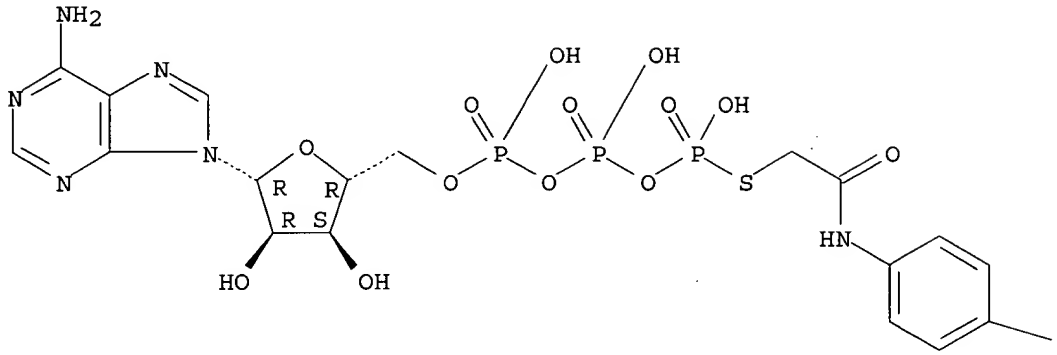

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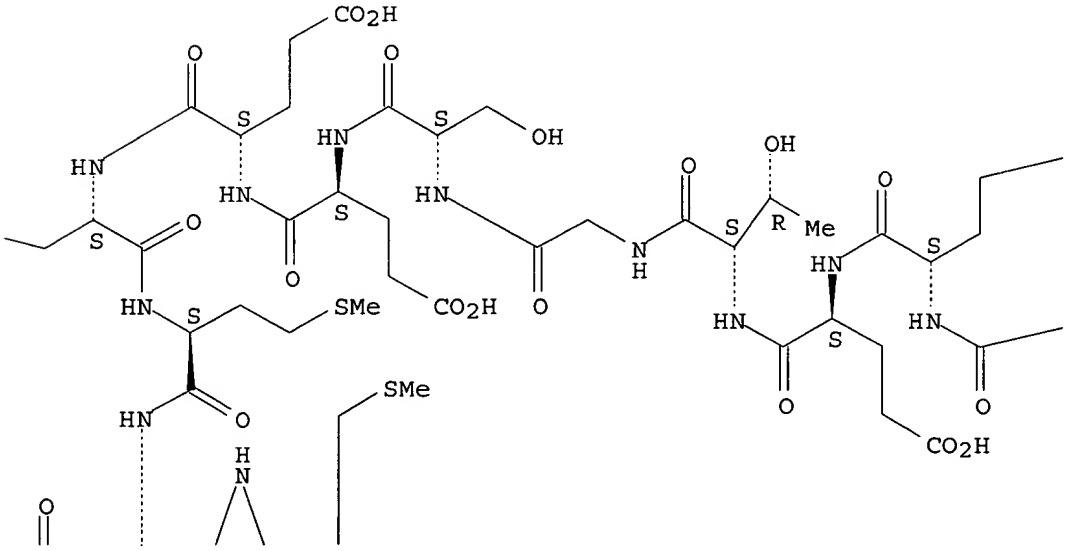

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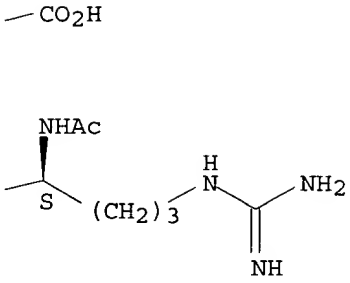

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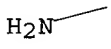

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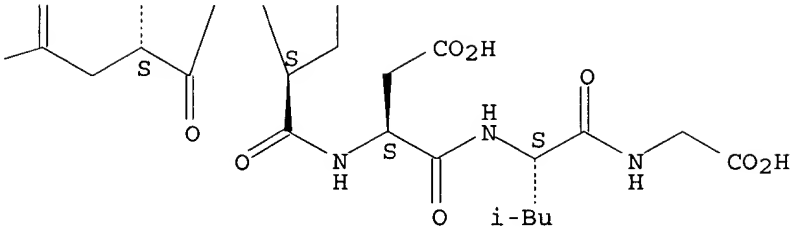

RN 863099-25-6 HCAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

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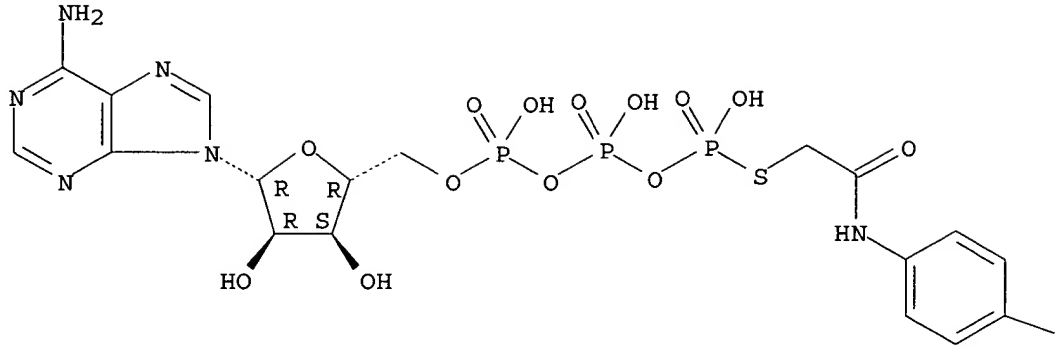

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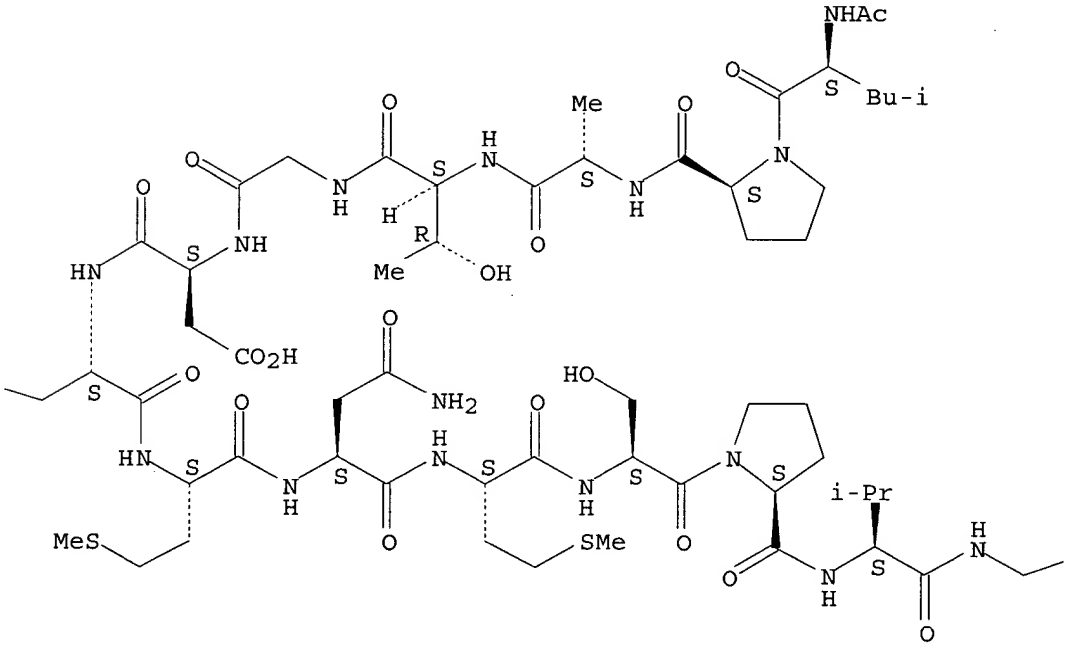

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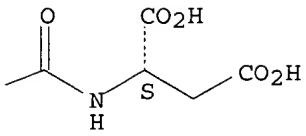

RN 863099-26-7 HCAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

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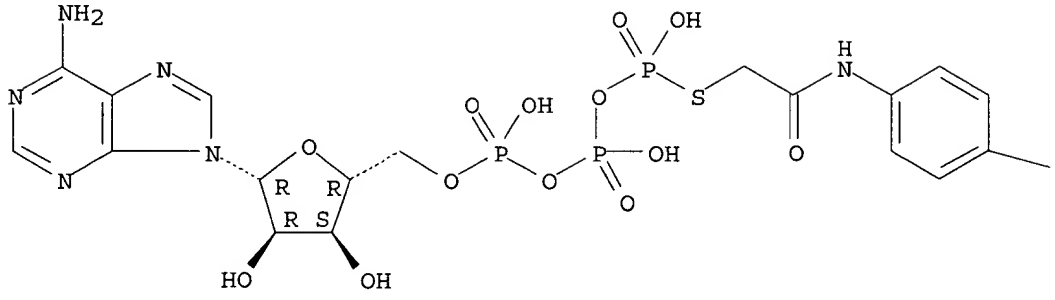

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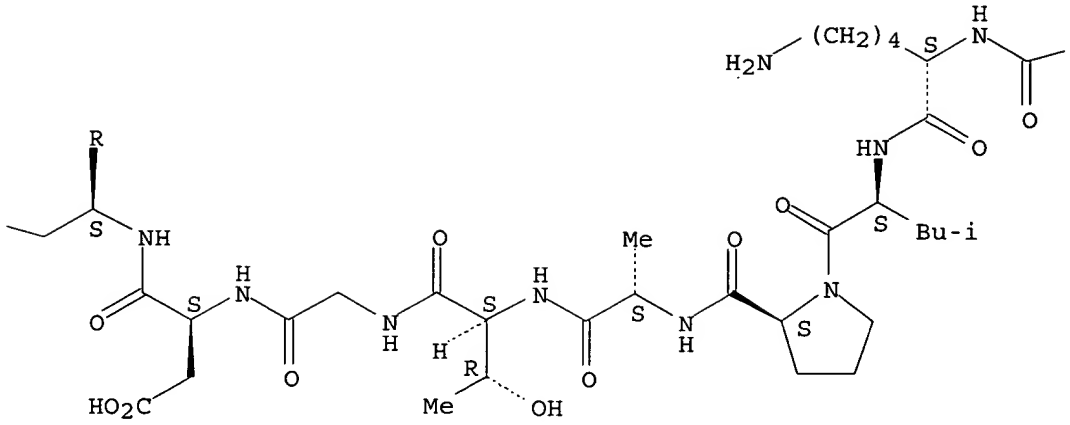

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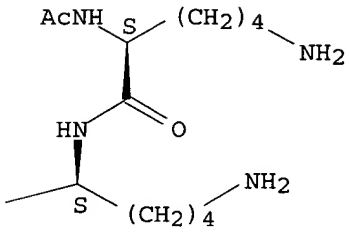

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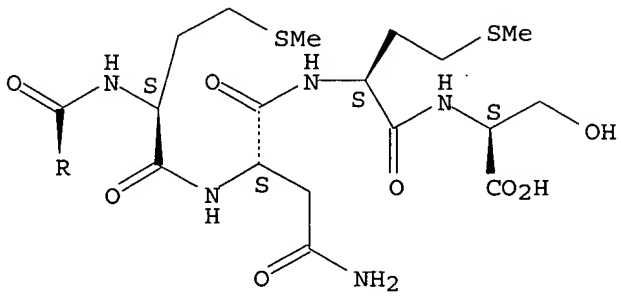

RN 863099-27-8 HCAPLUS
CN INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry.

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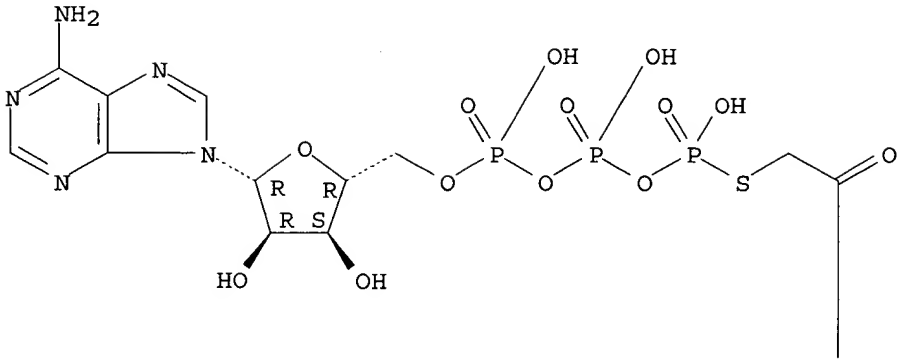

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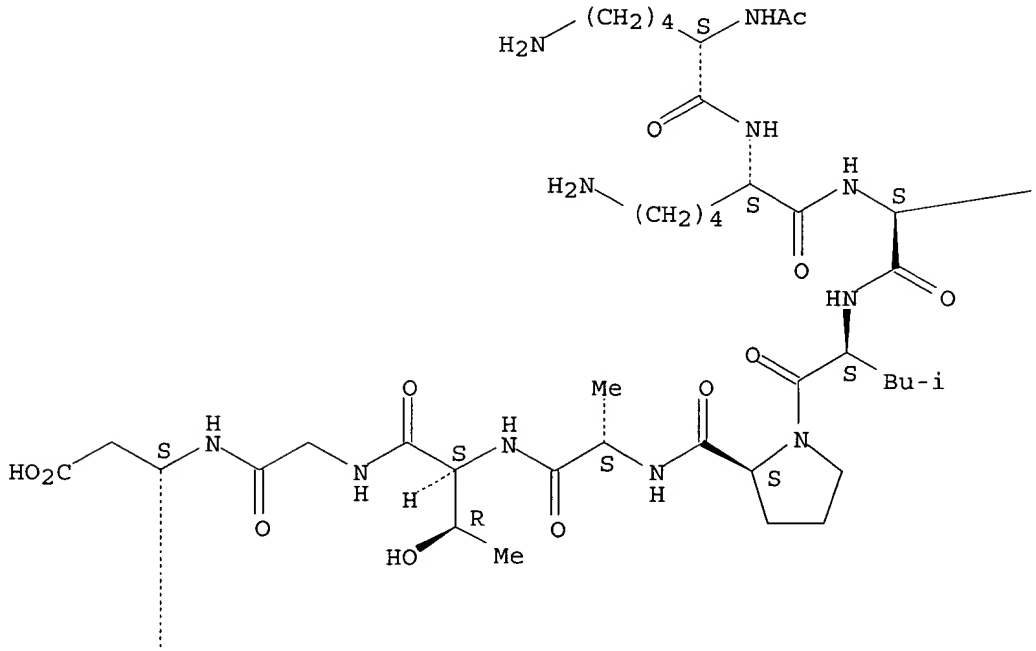

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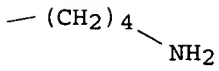

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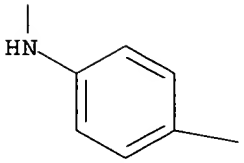

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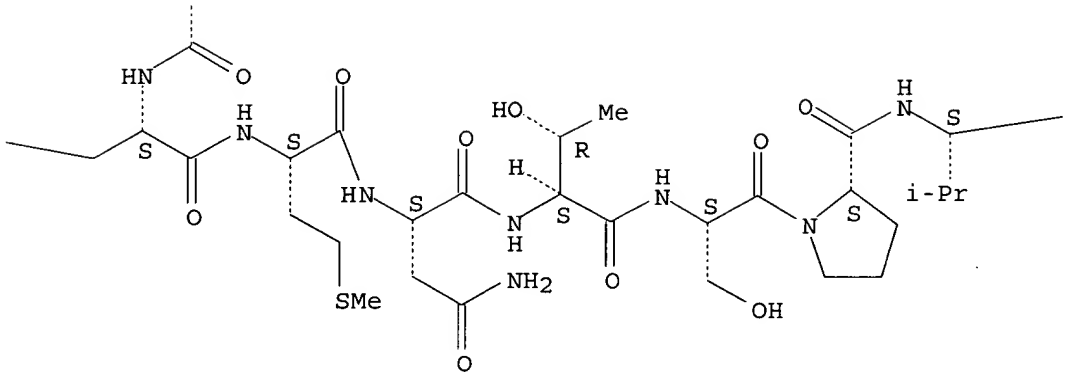

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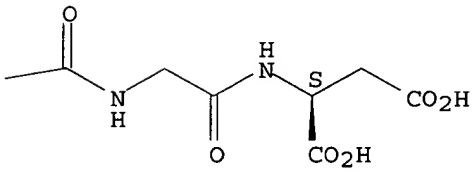


REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:958238 HCAPLUS

DOCUMENT NUMBER: 140:89809
TITLE: Conversion of a Tyrosine Kinase Protein Substrate to a High Affinity Ligand by ATP Linkage
AUTHOR(S): Shen, Kui; Cole, Philip A.
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Journal of the American Chemical Society (2003), 125(52), 16172-16173
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:89809

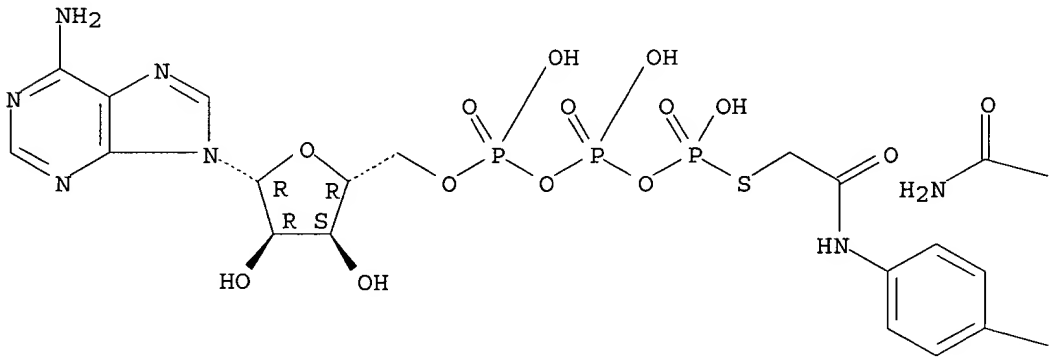
AB Protein kinases often show low affinity for their protein substrates, which makes it difficult to study kinase-substrate interactions. Here, the authors show using expressed protein ligation with the signaling protein Src that it is feasible to install a covalently linked ATP moiety into the tail of Src, generating a semisynthetic protein with a high affinity for its cognate tyrosine kinase, Csk. It is also established that this Src-ATP conjugate can be used to selectively pull down Csk from a complex protein mixture This work outlines a general strategy for identifying an unknown kinase that is responsible for the phosphorylation of a protein substrate on a site of interest.

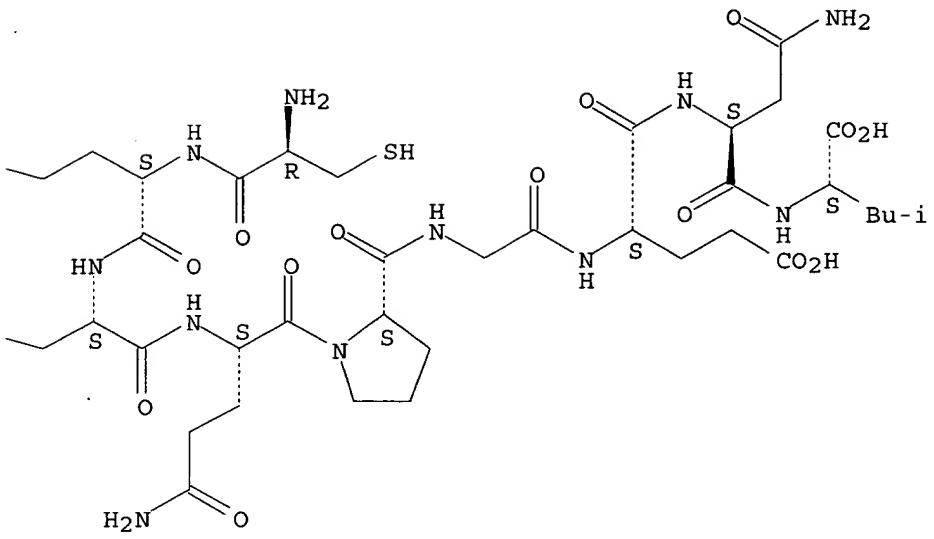
IT **643760-38-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(ATP linkage to Src-based peptide and expressed protein ligation to convert Csk tyrosine kinase substrate to high-affinity ligand/inhibitor for selective kinase pull down)

RN 643760-38-7 HCAPLUS
CN L-Leucine, L-cysteinyl-L-glutaminyl-4-[[6-(5'-adenylyloxy)-4,6-dihydroxy-4,6-dioxido-1-oxo-5-oxa-3-thia-4,6-diphosphahex-1-yl]amino]-L-phenylalanyl-L-glutaminyl-L-prolylglycyl-L-α-glutamyl-L-asparaginyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A





REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:713377 HCAPLUS
DOCUMENT NUMBER: 135:253738
TITLE: Bisubstrate inhibitors of kinases
INVENTOR(S): Courtney, Aliya; Cole, Philip A.; Parang, Keykavous; Abloogu, Ararat; Kohanski, Ron
PATENT ASSIGNEE(S): Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001070770	A2	20010927	WO 2001-US8886	20010321
WO 2001070770	A3	20020704		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002031820	A1	20020314	US 2001-811870	20010321
PRIORITY APPLN. INFO.:			US 2000-190799P	P 20000321

AB Protein kinase inhibitors have applications as anti-cancer therapeutic agents and biol. tools in cell signalling. Potent and selective bisubstrate inhibitors for the insulin receptor tyrosine kinase are based on a phosphoryl transfer mechanism involving a dissociative transition

state. One such inhibitor is synthesized by linking ATPγS to a peptide substrate analog via a two-carbon spacer. The compound is a high-affinity competitive inhibitor against both nucleotide and peptide substrate and shows a slow off-rate. A crystal structure of this inhibitor bound to the tyrosine kinase domain of the insulin receptor confirms the key design features inspired by a dissociative transition state, and reveal that the linker takes part in the octahedral coordination of an active site Mg2+ ion. A Kemptide-ATPγS compound was also prepared This compound was an inhibitor of protein kinase A.

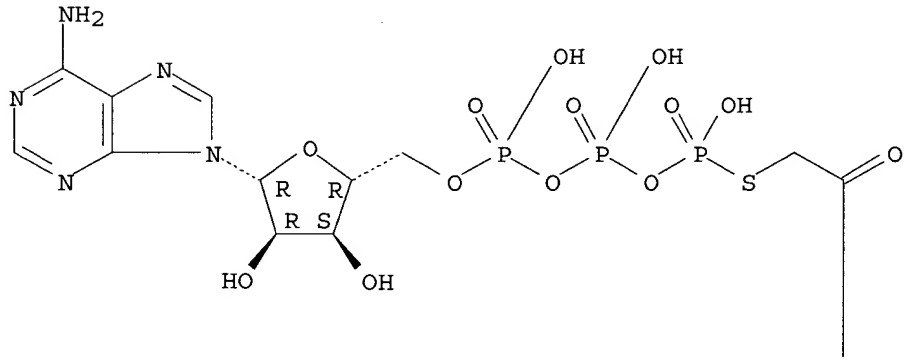
IT **329783-44-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(insulin receptor tyrosine kinase inhibitor; bisubstrate inhibitors of kinases)

RN 329783-44-0 HCAPLUS

CN L-Aspartic acid, N2-acetyl-L-lysyl-L-lysyl-L-lysyl-L-leucyl-L-prolyl-L-alanyl-L-threonylglycyl-L-α-aspartyl-4-[[6-(5'-adenylyloxy)-4,6-dihydroxy-4,6-dioxido-1-oxo-5-oxa-3-thia-4,6-diphosphahex-1-yl]amino]-L-phenylalanyl-L-methionyl-L-asparaginyl-L-methionyl-L-seryl-L-prolyl-L-valylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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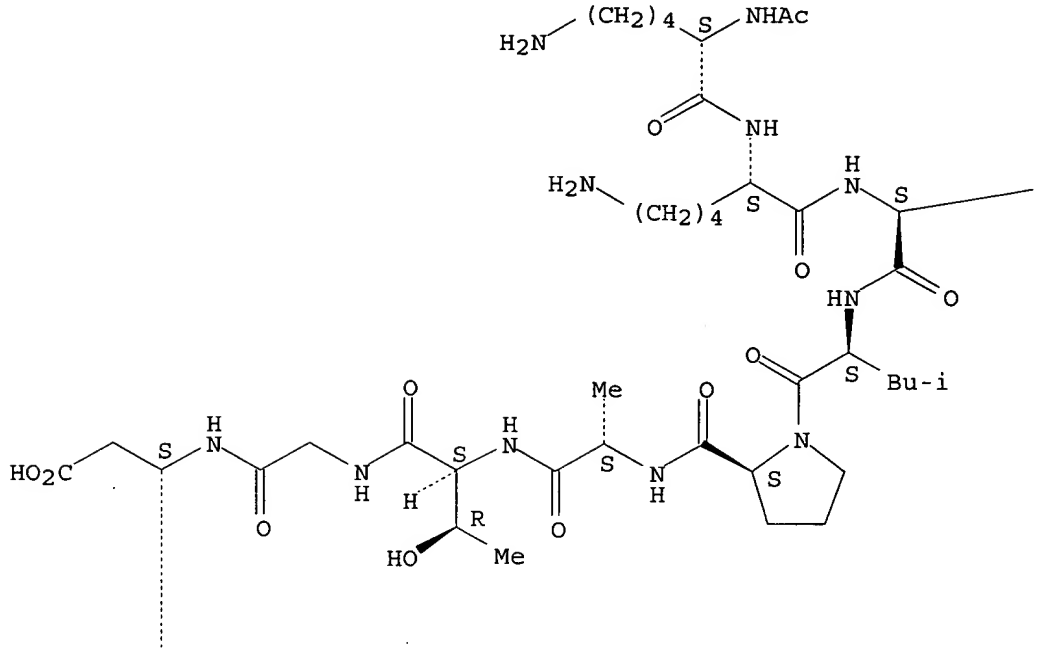

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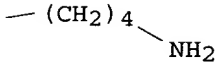

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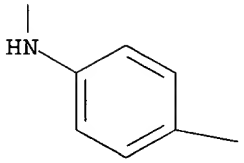

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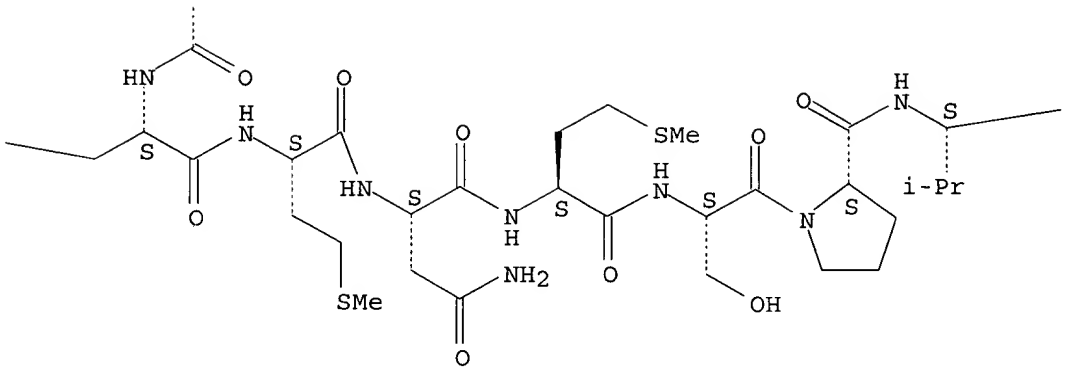

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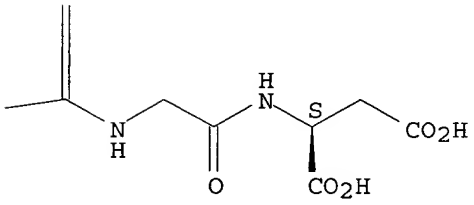


L22 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:37882 HCAPLUS
DOCUMENT NUMBER: 134:218831
TITLE: Mechanism-based design of a protein kinase inhibitor
AUTHOR(S): Parang, Keykavous; Till, Jeffrey H.; Ablooglu, Ararat J.; Kohanski, Ronald A.; Hubbard, Stevan R.; Cole, Philip A.
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Nature Structural Biology (2001), 8(1), 37-41
CODEN: NSBIEW; ISSN: 1072-8368
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Protein kinase inhibitors have applications as anticancer therapeutic agents and biol. tools in cell signaling. Based on a phosphoryl transfer mechanism involving a dissociative transition state, a potent and selective bisubstrate inhibitor for the insulin receptor tyrosine kinase

was synthesized by linking ATPγS to a peptide substrate analog via a two-carbon spacer. The compound was a high affinity competitive inhibitor against both nucleotide and peptide substrates and showed a slow off-rate. A crystal structure of this inhibitor bound to the tyrosine kinase domain of the insulin receptor confirmed the key design features inspired by a dissociative transition state, and revealed that the linker takes part in the octahedral coordination of an active site Mg2+. These studies suggest a general strategy for the development of selective protein kinase inhibitors.

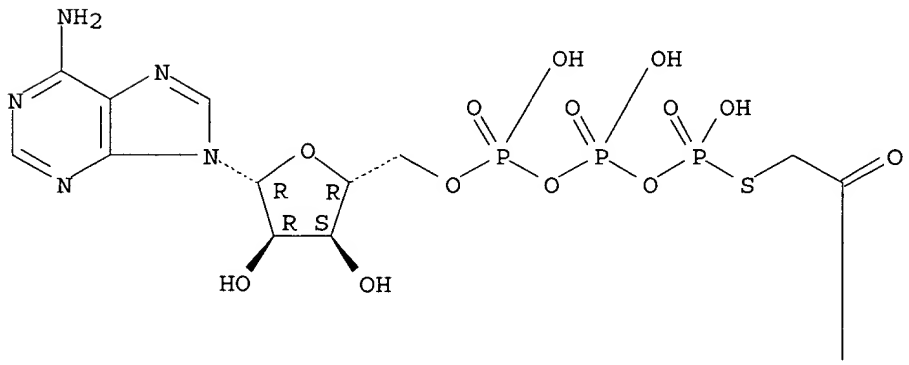
IT **329783-44-0D**, complexes with insulin receptor kinase
RL: PRP (Properties)
(crystal structure of bisubstrate inhibitor complexes with insulin receptor kinase)

RN 329783-44-0 HCAPLUS

CN L-Aspartic acid, N2-acetyl-L-lysyl-L-lysyl-L-lysyl-L-leucyl-L-prolyl-L-alanyl-L-threonylglycyl-L-α-aspartyl-4-[[6-(5'-adenylyloxy)-4,6-dihydroxy-4,6-dioxido-1-oxo-5-oxa-3-thia-4,6-diphosphahex-1-yl]amino]-L-phenylalanyl-L-methionyl-L-asparaginyl-L-methionyl-L-seryl-L-prolyl-L-valylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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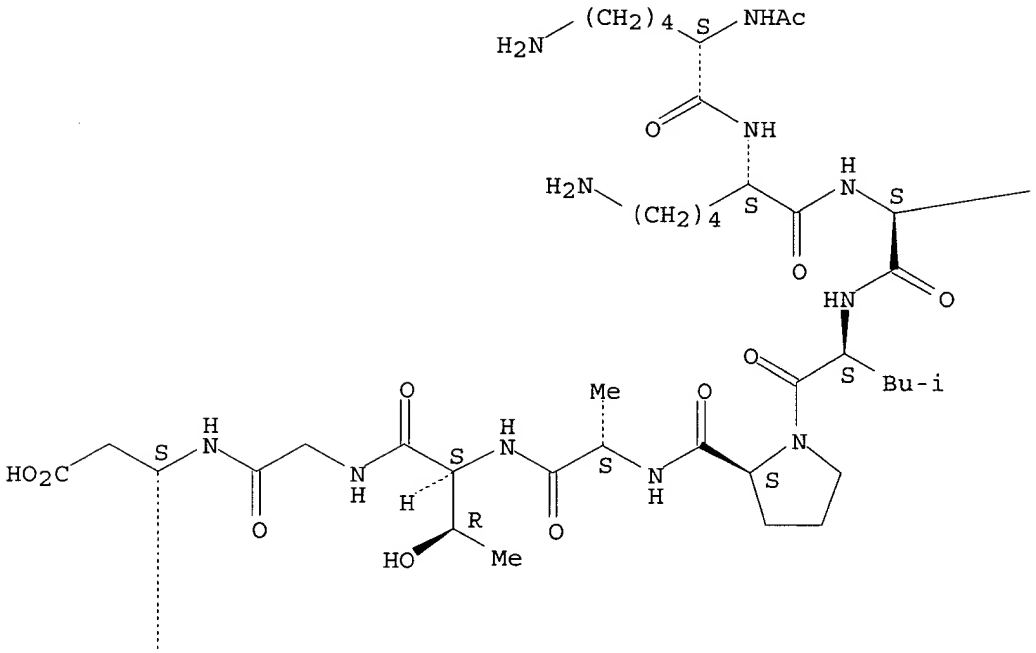

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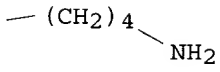

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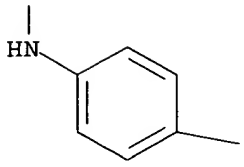

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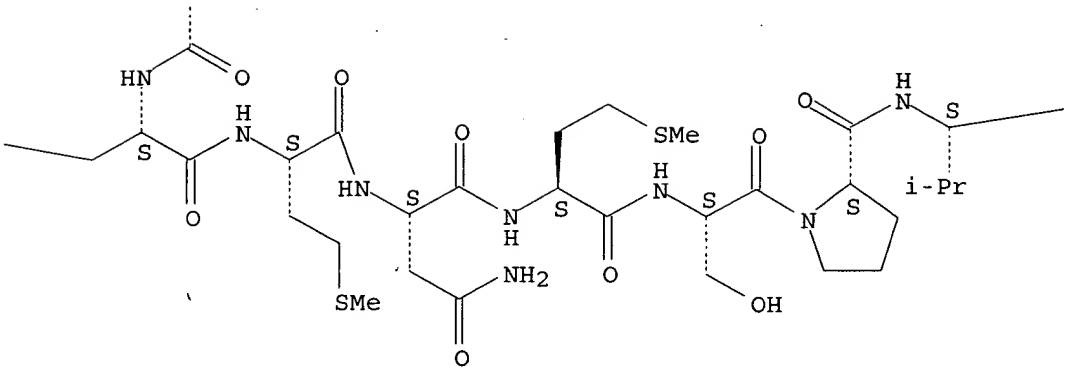

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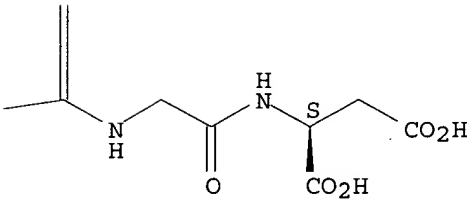
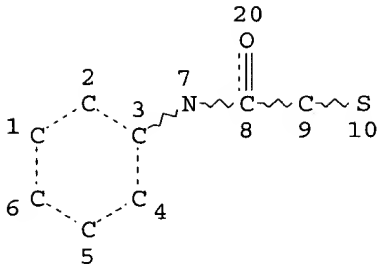


RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(mechanism-based design of bisubstrate inhibitor of insulin receptor kinase

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> => d stat que
L15 STR



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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 11

STEREO ATTRIBUTES: NONE
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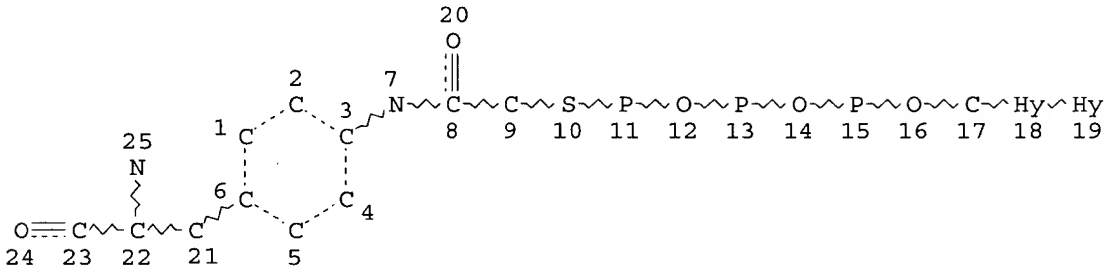
L18 STR



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DEFAULT MLEVEL IS ATOM
GGCAT IS MCY AT 18
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DEFAULT ECLEVEL IS LIMITED

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RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE
L19 6 SEA FILE=REGISTRY SUB=L17 SSS FUL L18
L20 45 SEA FILE=REGISTRY ABB=ON PLU=ON KKKLPATGD|MNMSPVGD/SQSP
L21 4 SEA FILE=REGISTRY ABB=ON PLU=ON ("INSULIN RECEPTOR KINASE"/CN OR "INSULIN RECEPTOR KINASE (SYCON RAPHANUS ISOFORM 1)"/CN OR "INSULIN RECEPTOR KINASE (SYCON RAPHANUS ISOFORM 2)"/CN OR "INSULIN RECEPTOR KINASE (SYCON RAPHANUS ISOFORM 3)"/CN)
L22 4 SEA FILE=HCAPLUS ABB=ON PLU=ON L19
L23 41 SEA FILE=HCAPLUS ABB=ON PLU=ON L20
L24 6708 SEA FILE=HCAPLUS ABB=ON PLU=ON L21 OR INSULIN(L)RECEPTOR(L)KINASE
L25 17 SEA FILE=HCAPLUS ABB=ON PLU=ON L24 AND L23
L26 14 SEA FILE=HCAPLUS ABB=ON PLU=ON L25 NOT L22

=> d ibib abs hitstr l26 1-14

L26 ANSWER 1 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:239208 HCAPLUS
DOCUMENT NUMBER: 142:311998
TITLE: Assaying transferase activity by using an artificial, multifunctional substrate comprising a small-molecule component linked to biopolymer-substrate-mimetic component
INVENTOR(S): Gellibolian, Robert; Rouhani, Riaz
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 66 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005024380	A2	20050317	WO 2004-US29004	20040903
WO 2005024380	A3	20050526		
WO 2005024380	C2	20050707		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-499863P P 20030903
OTHER SOURCE(S): MARPAT 142:311998

AB Embodiments of the present invention are directed to sensitive, specific, and com. feasible assays for transferase activity. Various embodiments of the present invention include artificial, multifunctional substrates specific for particular transferases that are chemical altered by the transferases to produce easily detectable, modified, multifunctional substrates. In one class of embodiments, the artificial, multifunctional substrate comprises a small-mol.-substrate component, or small-mol.-substrate-analog component, linked by a linking component to a biopolymer-substrate-mimetic or biopolymer-substrate-analog component. At least two, generally well-separated reporter moieties are included in the artificial, multifunctional substrate. The transferase, for which the artificial, multifunctional substrate is designed to serve as an assay reagent, catalyzes a generally covalent modification of the artificial, multifunctional substrate to produce a modified, artificial, multifunctional substrate reaction product in which the two reporter moieties are closely positioned to one another. When closely positioned to one another, the reporter moieties are detectable by one of various instrumental techniques. The artificial, multifunctional substrates for assaying protein kinase A, PCAF histone acetyltransferase, and protein arginine methyltransferase PRMT-1 are prepared

IT **848053-30-5**
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(biopolymer-substrate-mimetic component; transferase determination using

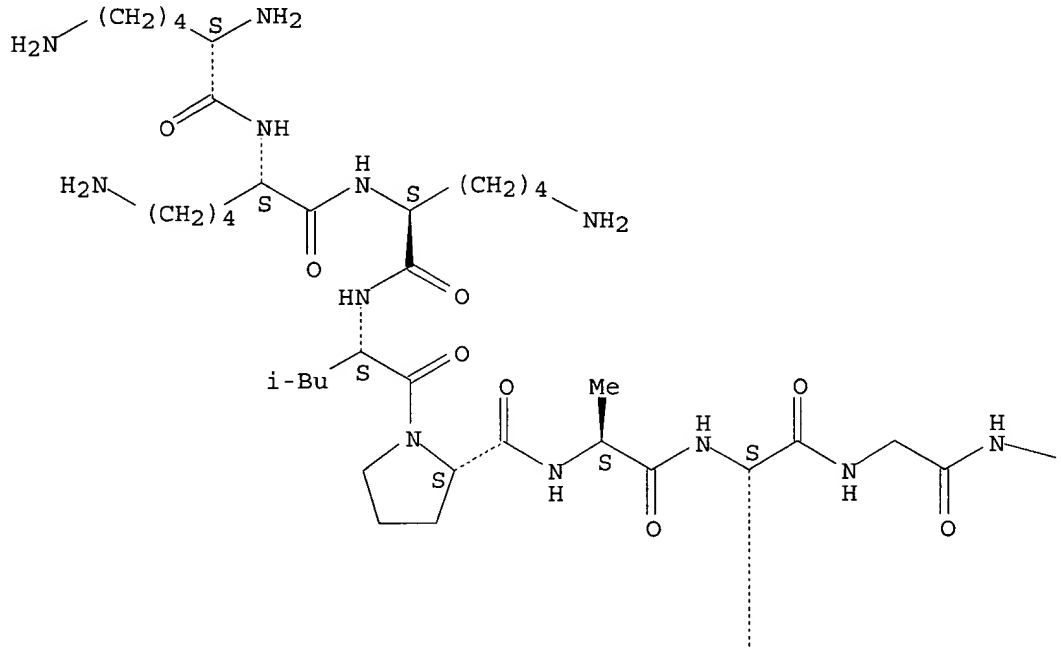
artificial, multifunctional substrate comprising small-mol. component linked to biopolymer-substrate-mimetic component)

RN 848053-30-5 HCAPLUS

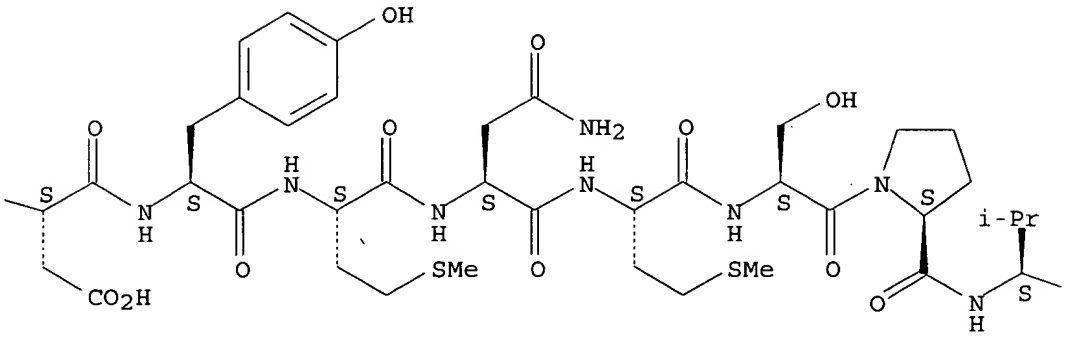
CN L-Aspartic acid, L-lysyl-L-lysyl-L-lysyl-L-leucyl-L-prolyl-L-alanyl-L-tyrosylglycyl-L-α-aspartyl-L-tyrosyl-L-methionyl-L-asparaginyl-L-methionyl-L-seryl-L-prolyl-L-valylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



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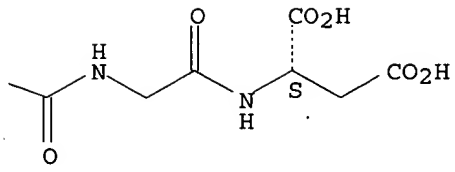
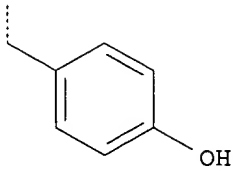


PAGE 2-A



IT **88201-45-0, Insulin receptor kinase**
RL: ANT (Analyte); ANST (Analytical study)
(transferase determination using artificial, multifunctional substrate comprising small-mol. component linked to biopolymer-substrate-mimetic component)
RN 88201-45-0 HCAPLUS
CN Kinase (phosphorylating), insulin receptor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L26 ANSWER 2 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:155467 HCAPLUS
DOCUMENT NUMBER: 142:236028
TITLE: A method for identification of **insulin receptor** substrate protein **kinase** inhibitors or agonists
INVENTOR(S): Tennagels, Norbert; Eckel, Juergen; Metzger, Sabine; Sommerfeld, Mark
PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE: Eur. Pat. Appl., 50 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1508806	A1	20050223	EP 2003-18517	20030816
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
WO 2005017196	A2	20050224	WO 2004-EP7900	20040716
WO 2005017196	A3	20050901		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005106653	A1	20050519	US 2004-918015	20040813
PRIORITY APPLN. INFO.:			EP 2003-18517 A	20030816
			US 2004-535139P P	20040108

AB The present invention provides a method for identification of **insulin receptor** substrate (IRS) protein **kinase** inhibitor or agonists. The detection kit contains PKC-ζ with IRS

peptide comprising PKC-ζ-Ser-phosphorylation site in the presence of putative inhibitor or agonist. To determine the IRS **kinase** inhibitor or agonist, the phosphorylation of PKC-ζ-Ser-phosphorylation site will be measured.

IT **845592-97-4**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; method for identification of **insulin receptor** substrate protein **kinase** inhibitors or agonists)
RN 845592-97-4 HCAPLUS
CN Kinase (phosphorylating), insulin receptor (rat 1235-amino acids) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **88201-45-0, Insulin receptor kinase**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(method for identification of **insulin receptor** substrate protein **kinase** inhibitors or agonists)
RN 88201-45-0 HCAPLUS
CN Kinase (phosphorylating), insulin receptor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 3 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:121193 HCAPLUS
DOCUMENT NUMBER: 142:214836
TITLE: Biomarkers of cyclin-dependent kinase modulation in cancer therapy
INVENTOR(S): Li, Martha; Rupnow, Brent A.; Webster, Kevin R.; Jackson, Donald G.; Wong, Tai W.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 141 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005012875	A2	20050210	WO 2004-US24424	20040729

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-490890P P 20030729
AB Biomarkers having expression patterns that correlate with a response of cells to treatment with one or more cdk modulating agents, and uses thereof. Transcription profiling was used to identify the biomarkers.

Specifically, transcription profiling of the effect of a certain cdk2 inhibitor (BMS 387032 0.5 L-tartaric acid salt) on peripheral blood mononuclear cells was first performed. Gene chips were used to quantitate the levels of gene expression on a large-scale with Affymetrix human gene chips HG-U95A, B, and C. Next, profiling of a cdk2 inhibitor-treated tumor cell line A28780 at multiple doses and time points was performed to establish a correlation of tumor site response with peripheral blood biomarkers. In order to establish the mol. target-specificity of the potential biomarkers, tumor cell line A2780 treated with anti-cdk2 oligonucleotides was also profiles. Overlapping gene expression changes were selected for further evaluation in human ovarian carcinoma xenograft A2780 that were treated with the cdk2 inhibitor. The selected biomarkers were subjected to real-time PCR anal. in order to verify the observed changes from the gene chip anal. The biomarker comprising GenBank accession number W28729 was discovered to have the most consistent and robust regulation in response to cdk inhibition. Provided are methods for testing or predicting whether a mammal will respond therapeutically to a method of treating cancer that comprises administering an agent that modulates cdk activity.

IT **841346-72-3**
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(amino acid sequence; biomarkers of cyclin-dependent kinase modulation in cancer therapy)
RN 841346-72-3 HCAPLUS
CN DNA (human clone WO2005012875-SEQID-2417 cyclin-dependent kinase modulator-regulated protein cDNA) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L26 ANSWER 4 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:1037263 HCAPLUS
DOCUMENT NUMBER: 142:19236
TITLE: Use of biotinylated peptides as substrates for the assay of protein kinases and protein phosphatases
INVENTOR(S): Tennagels, Norbert; Kannt, Aimo; Thuering, Harald
PATENT ASSIGNEE(S): Aventis Pharma Deutschland G.m.b.H., Germany
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004104220	A2	20041202	WO 2004-EP4428	20040427
WO 2004104220	A3	20050609		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10323081	A1	20041216	DE 2003-10323081	20030522

PRIORITY APPLN. INFO.: DE 2003-10323081 A 20030522

AB A method of using peptides derived from substrate domains of protein **kinases** and phosphatases is decribed. The substrate peptide is biotinylated to allow its capture by an immobilized avidin, either before or after incubation with the analyte enzyme. The change in the substrate, phosphorylation or dephosphorylation, can be determined after capture. The method is suitable for high throughput screening. Use of biotinylated peptides derived from **insulin receptor** substrate 1 as substrates for protein **kinase** C and **insulin receptor kinase** is demonstrated. Phosphorylation was quantified using com. ALPHAScreen technol.

IT **800916-52-3D**, biotinylated **800916-53-4D**, biotinylated
RL: ARU (Analytical role, unclassified); PRP (Properties); ANST (Analytical study)
(amino acid sequence, assay substrate; use of biotinylated peptides as substrates for assay of protein kinases and protein phosphatases)

RN 800916-52-3 HCAPLUS

CN 516-777-Protein, IRS-1 (insulin receptor substrate 1) (human) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 800916-53-4 HCAPLUS

CN Protein, IRS-1 (insulin receptor substrate 1) (human) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **88201-45-0**, **Insulin receptor kinase**
RL: ANT (Analyte); ANST (Analytical study)
(assays for; use of biotinylated peptides as substrates for assay of protein **kinases** and protein phosphatases)

RN 88201-45-0 HCAPLUS

CN Kinase (phosphorylating), insulin receptor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L26 ANSWER 5 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:847638 HCAPLUS

DOCUMENT NUMBER: 141:325696

TITLE: Genes showing altered levels of expression in response to inhibitors of cyclin-dependent kinases and their use in screening for novel inhibitors

INVENTOR(S): Green, Simon R.; Frame, Sheelagh; Blake, David

PATENT ASSIGNEE(S): Cyclacel Limited, UK

SOURCE: PCT Int. Appl., 175 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004087954	A2	20041014	WO 2004-GB1334	20040326
WO 2004087954	A3	20050127		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2003-7643 A 20030402

AB Genes that show changes in levels of expression in response to pharmaceutical inhibitors of cyclin-dependent kinases, especially 2,6,9-tri-substituted purines including roscovitine, are identified for use in the screening for roscovitine-like drugs using either animals or cultured cells. The identity of these markers facilitates the convenient identification of roscovitine-like activity both in vitro and in vivo.

IT **481200-98-0**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; genes showing altered levels of expression in response to inhibitors of cyclin-dependent kinases and their use in screening for novel inhibitors)

RN 481200-98-0 HCAPLUS

CN Insulin receptor substrate-1 (human gene insulin receptor substrate-1, IRS-1) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L26 ANSWER 6 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:392578 HCAPLUS

DOCUMENT NUMBER: 140:405486

TITLE: Polyclonal and monoclonal antibodies specific to phosphorylated insulin receptor substrate-1 and IRS-2 for diagnosis of type 2 diabetes mellitus

INVENTOR(S): Polakiewicz, Roberto; Wu, Jiong; Li, Yu

PATENT ASSIGNEE(S): Cell Signaling Technology, Inc., USA

SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004039963	A2	20040513	WO 2003-US34861	20031029
WO 2004039963	C1	20040729		
WO 2004039963	A3	20050317		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR

US 2004097713	A1	20040520	US 2003-694874	20031028

PRIORITY APPLN. INFO.: US 2002-422409P P 20021030

AB The invention discloses newly-discovered phosphorylation sites in human IRS-1 and IRS-2 at serine-1101 and serine-1149 resp., and provides antibodies, both polyclonal and monoclonal, that selectively bind to IRS-1 and/or IRS-2 when phosphorylated at these resp. sites, but do not bind to IRS-1 and/or IRS-2 when not phosphorylated at these resp. sites. The sites are relevant to insulin-resistance in type 2 diabetes. Also

provided are methods for determining the phosphorylation of IRS-1/2 or activity of PKC theta in a biol. sample, by using a detectable reagent, such as the disclosed antibodies, that binds to IRS-1/2 only when phosphorylated at Ser1101/Ser1149. Kits comprising the phosphoIRS-1/2 (Ser1101/1149) antibodies of the invention are also provided.

IT **688069-60-5D**, phosphorylated derivs. **688069-62-7D**, phosphorylated derivs.
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); BIOL (Biological study); USES (Uses)
(amino acid sequence; polyclonal and monoclonal antibodies specific to phosphorylated insulin receptor substrate-1 and IRS-2 for diagnosis of type 2 diabetes mellitus)

RN 688069-60-5 HCAPLUS

CN Protein IRS-1 (insulin receptor substrate 1) (human) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 688069-62-7 HCAPLUS

CN Protein IRS-1 (insulin receptor substrate 1) (mouse) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L26 ANSWER 7 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2000:722331 HCAPLUS

DOCUMENT NUMBER: 134:53060

TITLE: Probing the catalytic mechanism of the **insulin receptor kinase** with a tetrafluorotyrosine-containing peptide substrate

AUTHOR(S): Ablooglu, Ararat J.; Till, Jeffrey H.; Kim, Kyonghee; Parang, Keykavous; Cole, Philip A.; Hubbard, Stevan R.; Kohanski, Ronald A.

CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Mount Sinai School of Medicine, New York, NY, 10029, USA

SOURCE: Journal of Biological Chemistry (2000), 275(39), 30394-30398
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The interaction of a synthetic tetrafluorotyrosyl peptide substrate with the activated tyrosine **kinase** domain of the **insulin receptor** was studied by steady-state kinetics and x-ray crystallog. The pH-rate profiles indicate that the neutral phenol, rather than the chemical more reactive phenoxide ion, is required for enzyme-catalyzed phosphorylation. The pKa of the tetrafluorotyrosyl hydroxyl is elevated 2 pH units on the enzyme compared with solution, whereas the phenoxide anion species behaves as a weak competitive inhibitor of the tyrosine **kinase.** A structure of the binary enzyme-substrate complex shows the tetrafluorotyrosyl OH group at hydrogen bonding distances from the side chains of Asp1132 and Arg1136, consistent with elevation of the pKa. These findings strongly support a reaction mechanism favoring a dissociative transition state.

IT **88201-45-0D**, **Insulin receptor** tyrosine **kinase**, complexes with tetrafluorotyrosine-containing peptide substrate **143376-54-9D**, complexes with **insulin receptor** tyrosine **kinase**
RL: PRP (Properties)

(crystal structure; probing the catalytic mechanism of the **insulin receptor kinase** with a tetrafluorotyrosine-containing peptide substrate)

RN 88201-45-0 HCAPLUS

CN Kinase (phosphorylating), insulin receptor (9CI) (CA INDEX NAME)

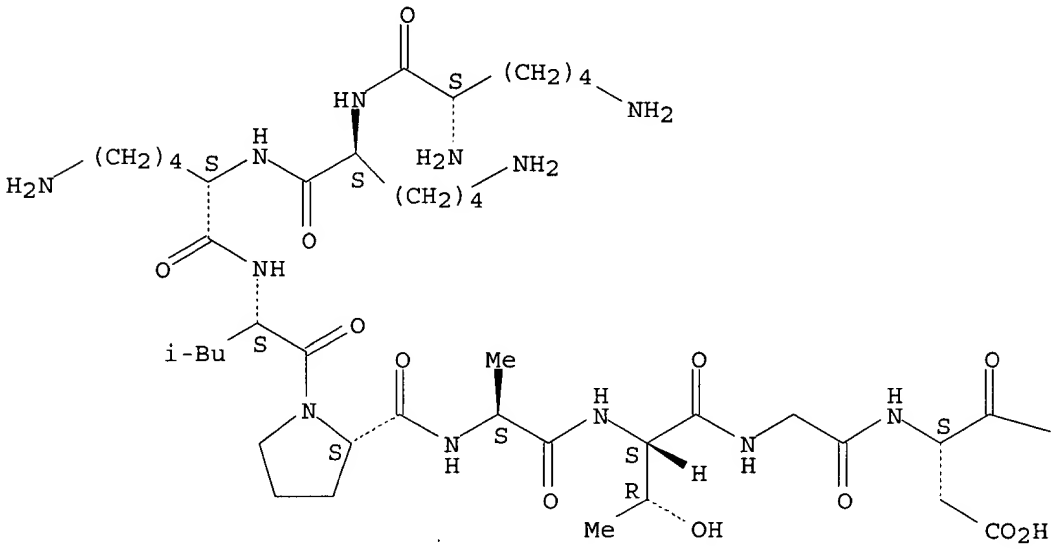
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 143376-54-9 HCAPLUS

CN L-Aspartic acid, L-lysyl-L-lysyl-L-lysyl-L-leucyl-L-prolyl-L-alanyl-L-threonylglycyl-L-α-aspartyl-L-tyrosyl-L-methionyl-L-asparaginyl-L-methionyl-L-seryl-L-prolyl-L-valylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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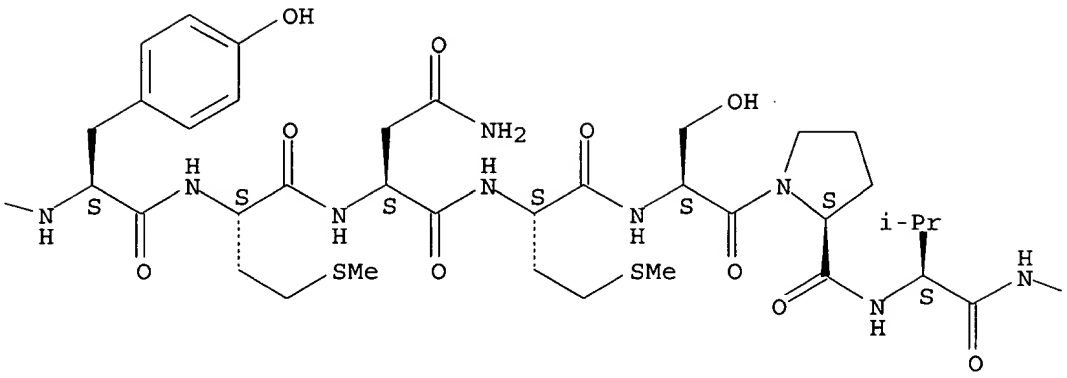

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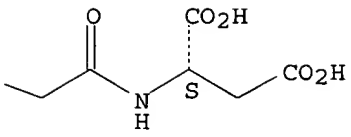
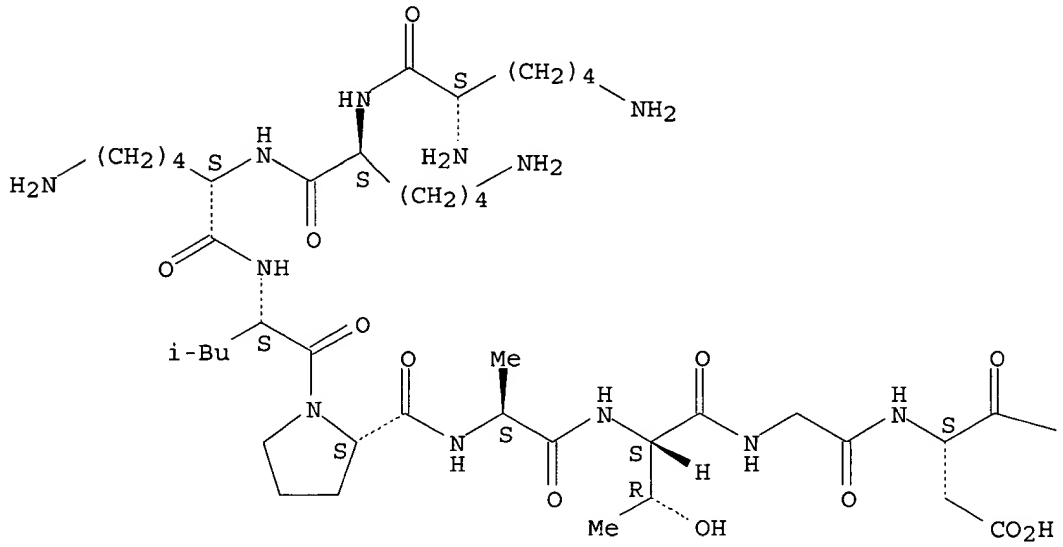


IT **143376-54-9**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(probing the catalytic mechanism of the **insulin receptor kinase** with a tetrafluorotyrosine-containing peptide substrate)

RN 143376-54-9 HCAPLUS
CN L-Aspartic acid, L-lysyl-L-lysyl-L-lysyl-L-leucyl-L-prolyl-L-alanyl-L-threonylglycyl-L-α-aspartyl-L-tyrosyl-L-methionyl-L-asparaginyl-L-methionyl-L-seryl-L-prolyl-L-valylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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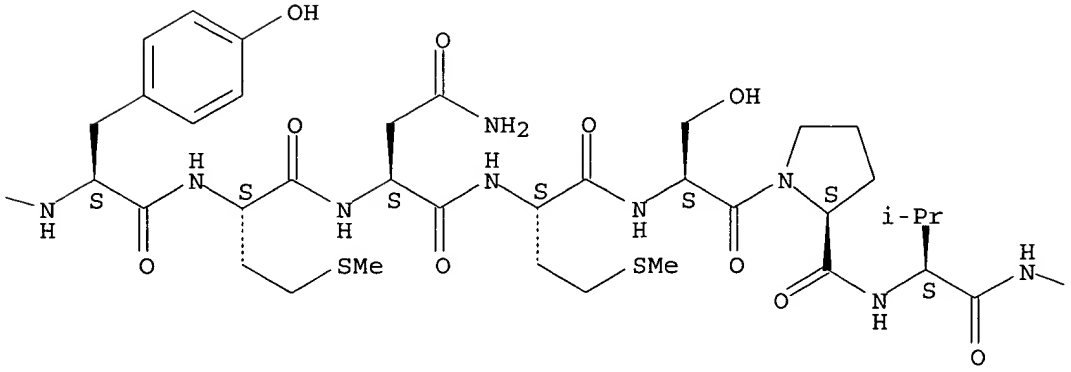
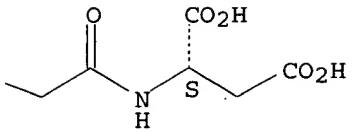




IT **88201-45-0**, **Insulin receptor** tyrosine **kinase**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(probing the catalytic mechanism of the **insulin receptor kinase** with a tetrafluorotyrosine-containing peptide substrate)
RN 88201-45-0 HCAPLUS
CN Kinase (phosphorylating), insulin receptor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 8 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1997:651550 HCAPLUS
DOCUMENT NUMBER: 127:328319
TITLE: Crystal structure of the activated **insulin receptor** tyrosine **kinase** in complex with peptide substrate and ATP analog
AUTHOR(S): Hubbard, Stevan R.
CORPORATE SOURCE: Dep. Pharm., Skirball Inst. Biomol. Med., New York Univ. Med. Cent., New York, NY, 10016, USA
SOURCE: EMBO Journal (1997), 16(18), 5572-5581
CODEN: EMJODG; ISSN: 0261-4189
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The crystal structure of the phosphorylated, activated form of **insulin receptor** tyrosine **kinase** (I) in complex with an 18-residue peptide substrate (KKKLPATGDYMNMSPVGD), and the nonhydrolyzable ATP analog, AMP-PNP, was determined at 1.9 Å resolution The activation loop (A-loop) of I undergoes a major conformational change upon autophosphorylation of Tyr-1158, Tyr-1162, and Tyr-1163 within the loop, resulting in unrestricted access of ATP and protein substrates to the I

active site. Phosphorylated Tyr-1163 (pTyr-1163) was the key phospho-Tyr group in stabilizing the conformation of the tris-phosphorylated A-loop, whereas pTyr-1158 was completely solvent-exposed, suggesting an availability for interaction with downstream signaling proteins. The YMXM-containing peptide substrate bound as a short anti-parallel β-strand to the C-terminal end of the A-loop, with the Met side-chains occupying 2 hydrophobic pockets on the C-terminal lobe of I. The structure thus reveals the mol. basis for **insulin receptor** activation via autophosphorylation, and provides insights into I substrate specificity and the mechanism of phosphotransfer.

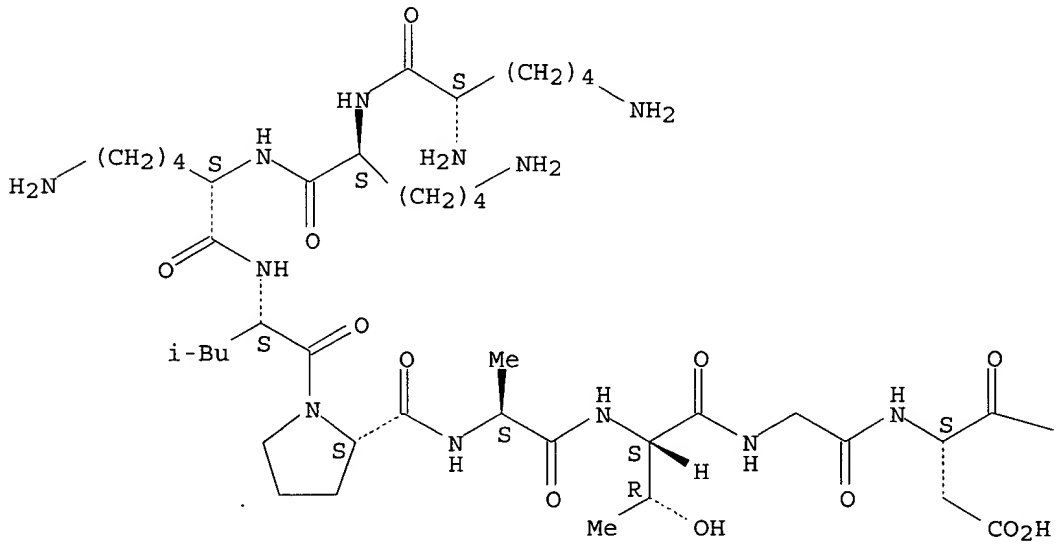
IT **88201-45-0D**, **Insulin receptor kinase**
, complexes with peptide substrate and ATP analog **143376-54-9D**, complexes with **insulin receptor kinase** and ATP analog
RL: PRP (Properties)
(crystal structure of activated **insulin receptor kinase** in complex with a peptide substrate and an ATP analog)

RN 88201-45-0 HCAPLUS
CN Kinase (phosphorylating), insulin receptor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 143376-54-9 HCAPLUS
CN L-Aspartic acid, L-lysyl-L-lysyl-L-lysyl-L-leucyl-L-prolyl-L-alanyl-L-threonylglycyl-L-α-aspartyl-L-tyrosyl-L-methionyl-L-asparaginyl-L-methionyl-L-seryl-L-prolyl-L-valylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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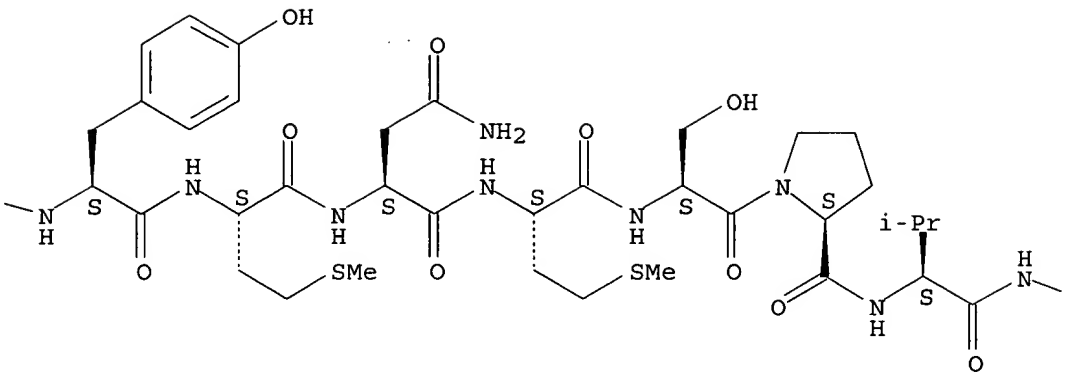

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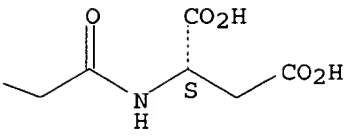


REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 9 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:1001748 HCAPLUS
DOCUMENT NUMBER: 124:80394
TITLE: Substrate specificities of the **insulin** and

insulin-like growth factor 1 **receptor** tyrosine **kinase** catalytic domains

AUTHOR(S): Xu, Bin; Bird, Vincent G.; Miller, W. Todd
CORPORATE SOURCE: Sch. Med., State Univ. New York, Stony Brook, NY, 11794, USA
SOURCE: Journal of Biological Chemistry (1995), 270(50), 29825-30
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To compare the substrate specificities of the **insulin** and **insulin**-like growth factor 1 (IGF-1) **receptor** tyrosine **kinases**, the catalytic domains of the enzymes have been expressed in Escherichia coli as fusion proteins. The purified proteins have **kinase** activity, demonstrating that the catalytic domain of IGF-1 **receptor**, like that of **insulin receptor**, is active independent of its ligand-binding and transmembrane domains. The specificities of the two enzymes for the divalent cations Mg2+ and Mn2+ are indistinguishable. A series of peptides has been prepared that reproduces the major phosphorylation sites of **insulin receptor** substrate-1, a common substrate for the two **receptor** tyrosine **kinases** in vivo. **Insulin** and IGF-1 **receptors** show distinct preferences for these peptides; whereas **insulin receptor** prefers peptides based on Tyr-987 or Tyr-727 of **insulin receptor** substrate-1, the IGF-1 **receptor** preferentially recognizes the Tyr-895 site. The latter site, when phosphorylated, is a binding site for the SH2 domain-containing adaptor protein Grb2. The ability of the two **receptor** tyrosine **kinases** to be phosphorylated and activated by v-Src has also been examined The catalytic activity of IGF-1 **receptor** is stimulated ≈3.4-fold by treatment with purified v-Src, while **insulin receptor** shows very little effect of Src phosphorylation under these conditions. This observation is relevant to recent findings of IGF-1 **receptor** activation in Src-transformed cells, and may represent one method by which Src amplifies its mitogenic signal. Collectively the data suggest that the catalytic domains of the two **receptor kinases** possess inherently different substrate specificities and signaling potentials.

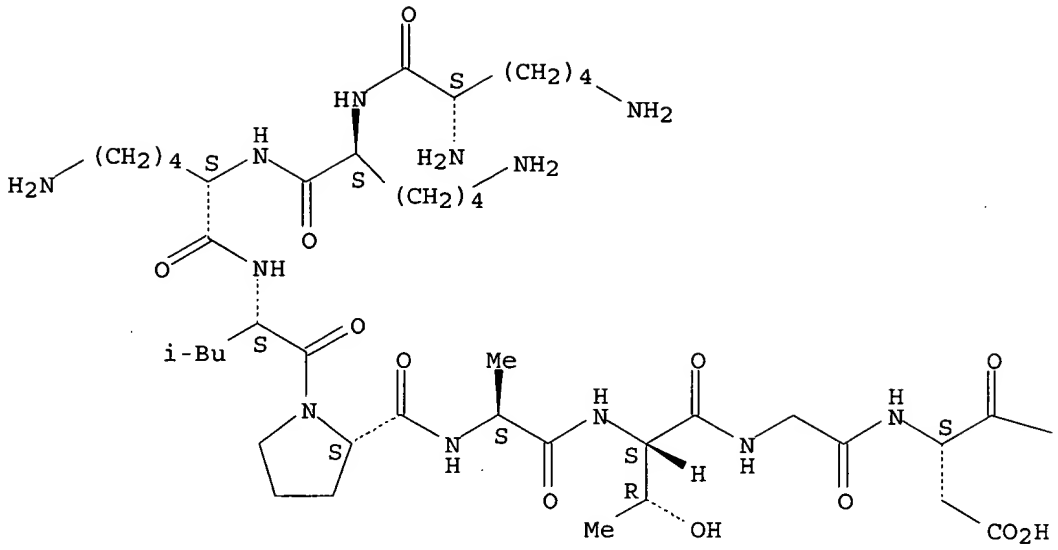
IT **143376-54-9**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(differential substrate specificities of the **insulin** **receptor** and **insulin**-like growth factor 1 **receptor** tyrosine **kinase** catalytic domains)

RN 143376-54-9 HCAPLUS

CN L-Aspartic acid, L-lysyl-L-lysyl-L-lysyl-L-leucyl-L-prolyl-L-alanyl-L-threonylglycyl-L-α-aspartyl-L-tyrosyl-L-methionyl-L-asparaginyl-L-methionyl-L-seryl-L-prolyl-L-valylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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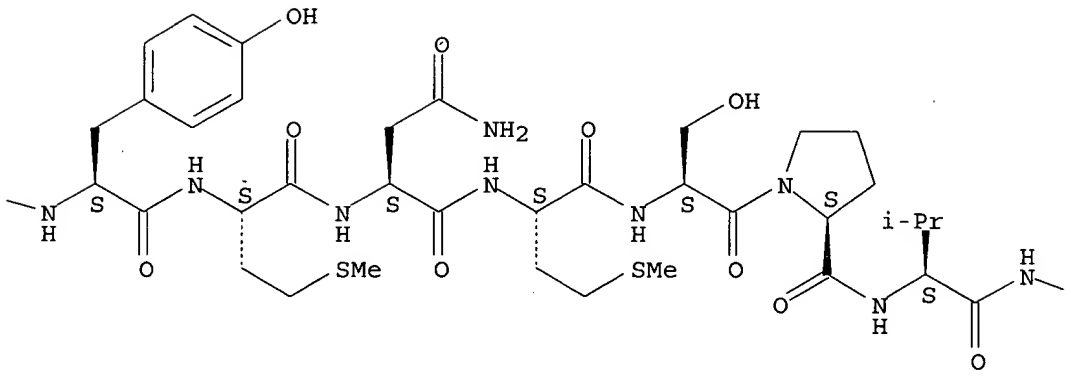
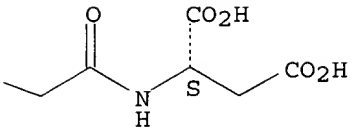




IT **88201-45-0**, **Insulin receptor** tyrosine **kinase**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(recombinant; differential substrate specificities of the **insulin receptor** and **insulin**-like growth factor 1 **receptor** tyrosine **kinase** catalytic domains)
RN 88201-45-0 HCAPLUS
CN Kinase (phosphorylating), insulin receptor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L26 ANSWER 10 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1994:97466 HCAPLUS
DOCUMENT NUMBER: 120:97466
TITLE: Human skeletal muscle insulin receptor substrate-1: characterization of the cDNA, gene, and chromosomal localization
AUTHOR(S): Araki, Eiichi; Sun, Xiao Jian; Haag, Burritt L., III; Chuang, Lee Ming; Zhang, Yitao; Yang-Feng, Teresa L.; White, Morris F.; Kahn, C. Ronald
CORPORATE SOURCE: Res. Div., Joslin Diabetes Cent., Boston, MA, 02215, USA
SOURCE: Diabetes (1993), 42(7), 1041-54
CODEN: DIAEAZ; ISSN: 0012-1797
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Insulin receptor** substrate-1 is a major substrate of **insulin receptor** Tyr **kinase.** We have now cloned the IRS-1 cDNA from human skeletal muscle, one of the most important target tissues of **insulin** action, localized and cloned the human IRS-1 gene, and studied the expression of the protein in Chinese hamster ovary cells. Human IRS-1 cDNA encodes a 1242 amino acid sequence

that is 88% identical to rat liver IRS-1. The 14 potential Tyr phosphorylation sites include 6 Tyr-Met-X-Met motifs and 3 Tyr-X-X-Met motifs that are completely conserved in human IRS-1. Human IRS-1 has >50 possible Ser/Thr phosphorylation sites and one potential ATP-binding site close to the NH2-terminal. The human IRS-1 gene contains the entire 5'-untranslated region and protein coding region in a single exon and was localized on chromosome 2 q36-37 by in situ hybridization. By Northern blot anal., IRS-1 mRNA is rare and consists of two species of 6.9 and 6 kilobase. By using quant. polymerase chain reaction after reverse transcription of total RNA from human fetal tissues, IRS-1 mRNA could be identified in all tissues. When human IRS-1 cDNA was expressed in Chinese hamster ovary cells, the protein migrated between 170,000-180,000 Mr in sodium dodecyl sulfate-polyacrylamide gel electrophoresis and was rapidly Tyr phosphorylated upon **insulin** stimulation. Thus, IRS-1 is widely expressed and highly conserved across species and tissues. Compared with rat protein, human IRS-1 contains more potential Ser/Thr phosphorylation sites and only one nucleotide binding site. The entire protein encoding sequence is contained within a single exon.

IT **151086-85-0**, Phosphoprotein (human clone λE36 insulin receptor substrate 1 protein moiety)
RL: PRP (Properties)
(amino acid sequence and tyrosine phosphorylation sites of)

RN 151086-85-0 HCAPLUS

CN Phosphoprotein IRS-1 (human clone λE36 reduced) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **151086-86-1**, Phosphoprotein IRS-1 (human clone γE1 insulin receptor substrate 1 reduced) **151086-87-2**, Phosphoprotein IRS-1 (human clone λE5 insulin receptor substrate 1 reduced)
RL: PRP (Properties)
(amino acid sequence of)

RN 151086-86-1 HCAPLUS

CN Phosphoprotein IRS-1 (human clone γE1 reduced) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 151086-87-2 HCAPLUS

CN Phosphoprotein IRS-1 (human clone λE5 reduced) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L26 ANSWER 11 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1993:620273 HCAPLUS

DOCUMENT NUMBER: 119:220273

TITLE: Phosphorylation of synthetic peptides containing Tyr-Met-X-Met motifs by nonreceptor tyrosine kinases in vitro

AUTHOR(S): Garcia, Pilar; Shoelson, Steven E.; George, Shaji T.; Hinds, Duane A.; Goldberg, Allan R.; Miller, W. Todd

CORPORATE SOURCE: Sch. Med., State Univ. New York, Stony Brook, NY, 11794, USA

SOURCE: Journal of Biological Chemistry (1993), 268(33), 25146-51
CODEN: JBCHA3; ISSN: 0021-9258

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Several tyrosine phosphorylation sites in the **insulin receptor kinase** substrate, protein IRS-1, are predicted

to be within Tyr-Met-X-Met (YMXM) motifs, and synthetic peptides corresponding to these sequences are excellent substrates for the **insulin receptor kinase** in vitro. Here, synthetic YMXM-containing peptides are shown to act as substrates for 2 members of the nonreceptor subfamily of tyrosine **kinases**, v-Src and v-Abl (the transforming gene products of Rous sarcoma virus and Abelson murine leukemia virus, resp.). For v-Src, a baculovirus expression system was used which was capable of producing milligram quantities of pure 60-kDa v-Src in Spodoptera frugiperda (Sf9) cells. The source of v-Abl was an Escherichia coli expression vector that produces a fusion protein of glutathione S-transferase with the abl catalytic domain. The synthetic YMXM-containing peptides had among the highest apparent affinities described to date for either tyrosine **kinase**, with Km values as low as 97 μM for v-Src and v-Abl. Comparisons with the results obtained with the **insulin receptor kinase** revealed differences in substrate specificity among the enzymes. In particular, v-Src was more tolerant of substitutions at the Met+1 and Met+3 positions in the YMXM motif than either v-Abl or the **insulin receptor kinase** but was more dependent on the presence of a preceding acidic amino acid. For v-Abl, the presence of threonine at any position in the YMXM motif caused a reduction in catalytic efficiency. Phosphorylated YMXM motifs were recognition elements for binding to the src homol. 2 (SH2) domains of phosphatidylinositol 3'-**kinase** and addnl. proteins; hence, differences in specificity of tyrosine **kinases** toward YMXM-containing proteins may have relevance to downstream signaling events.

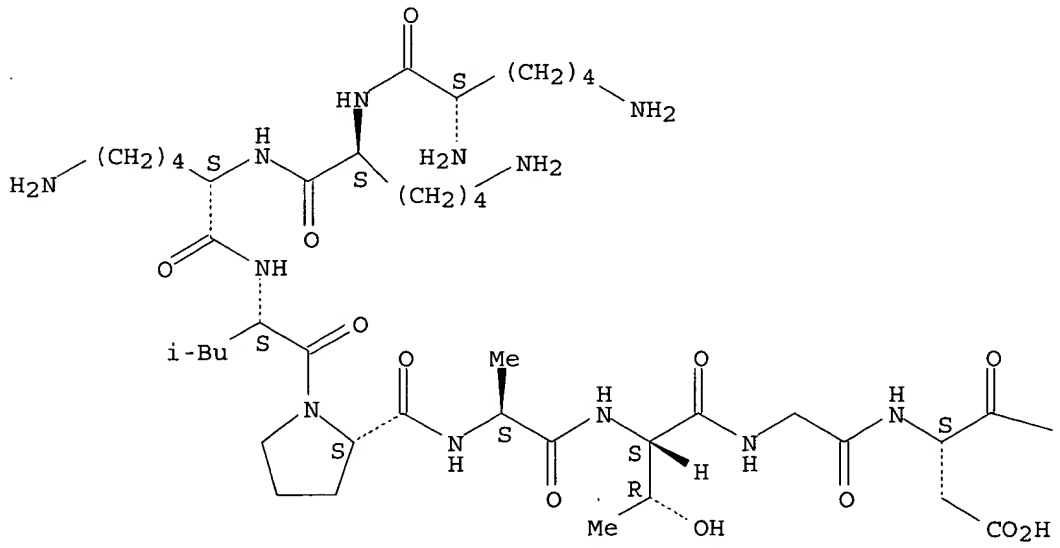
IT **143376-54-9**
RL: BIOL (Biological study)
(phosphorylation of, by protein tyrosine kinases, kinetics of)

RN 143376-54-9 HCAPLUS

CN L-Aspartic acid, L-lysyl-L-lysyl-L-lysyl-L-leucyl-L-prolyl-L-alanyl-L-threonylglycyl-L-α-aspartyl-L-tyrosyl-L-methionyl-L-asparaginyl-L-methionyl-L-seryl-L-prolyl-L-valylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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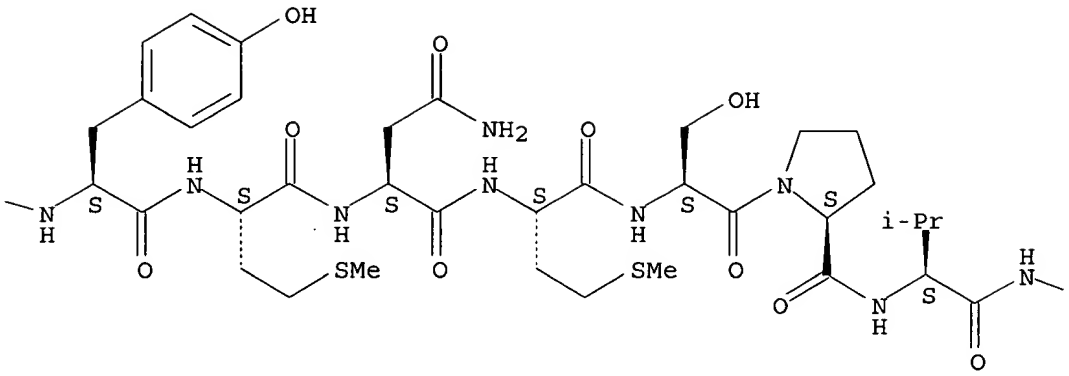

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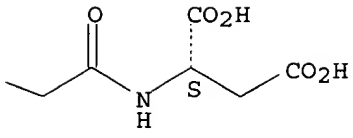


L26 ANSWER 12 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:402479 HCAPLUS
DOCUMENT NUMBER: 119:2479
TITLE: Nucleic acid encoding insulin receptor substrate-1 (IRS-1), IRS-1 protein, diseases, therapy associated

with the metabolism of IRS-1
INVENTOR(S): Kahn, C. Ronald; White, Morris F.; Rothenberg, Paul Louis
PATENT ASSIGNEE(S): Joslin Diabetes Center, Inc., USA
SOURCE: PCT Int. Appl., 134 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9213083	A1	19920806	WO 1992-US437	19920117
W: JP				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE				
EP 572508	A1	19931208	EP 1992-906151	19920117
R: CH, DE, DK, LI				
US 5260200	A	19931109	US 1992-962023	19921015
US 5621075	A	19970415	US 1993-94948	19930721
PRIORITY APPLN. INFO.:			US 1991-643982 A	19910118
			WO 1992-US437 W	19920117
			US 1992-962023 A3	19921015

AB Mammalian IRS-1 cDNA is cloned and sequenced. This cDNA may be expressed in cells to prepare IRS-1. **Insulin**-related diseases such as diabetes may be diagnosed by measuring aspects of IRS-1 metabolism, e.g. measurement of IRS-1 levels, level of phosphorylation of IRS-1, or **kinase** activity of IRS-1 (no data). Similar measurements may be used to assay the effects of therapeutic agents (no data). Therapeutic treatment of mammals by altering IRS-1 metabolism is claimed. Rat liver IRS-1 cDNA was cloned and sequenced. Phosphorylation of **insulin receptor** and intracellular proteins was examined Pp185, called IRS-1, was found to be phosphorylated by the **receptor.** Phosphatidyl inositol 3-**kinase** activity was associated with the purified IRS-1.

IT **145559-05-3**, Phosphoprotein IRS 1 (rat clone C18/P2-2)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence of, complete, cloning of cDNA for)

RN 145559-05-3 HCAPLUS
CN Phosphoprotein IRS 1 (rat clone C18/P2-2) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L26 ANSWER 13 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:527074 HCAPLUS
DOCUMENT NUMBER: 117:127074
TITLE: YMXM motifs of IRS-1 define substrate specificity of the **insulin receptor kinase**
AUTHOR(S): Shoelson, Steven E.; Chatterjee, Swati; Chaudhuri, Manas; White, Morris F.
CORPORATE SOURCE: Brigham Women's Hosp., Harvard Med. Sch., Boston, MA, 02215, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1992), 89(6), 2027-31
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Of 34 tyrosine residues in **insulin receptor** substrate

1 (IRS-1), 14 are adjacent to acidic residues, suggesting that they might be phosphorylation sites. Synthetic peptides corresponding to sequences surrounding these tyrosines were used as substrates of the **insulin receptor kinase.** Surprisingly six of these, each within YMXM motifs, were phosphorylated with greatest efficiency (Km, 24-92 μM; kcat/Km,0.6-2.1 + 104M-1 sec-1). Substituted YMXM peptides revealed a strong preference of the **insulin receptor kinase** for methionine at Y + 1 and Y + 3 positions. When phosphorylated, related YMXM sequences are recognition motifs for binding to proteins with src-homol. (SH2) domains. The combined hydrophobic and flexible nature of methionine side chains adjacent to the targeted tyrosines provides a versatile contact for recognition by diverse proteins involved in signal transduction.

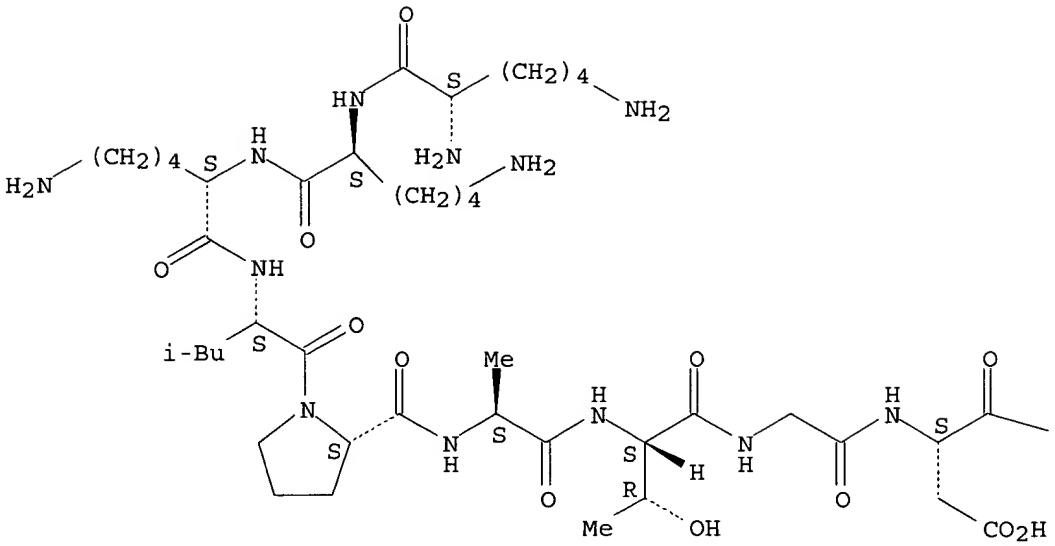
IT **141349-62-4**, Phosphoprotein IRS 1 (rat clone C18/S27 protein moiety reduced)
RL: BIOL (Biological study)
(YMXM motifs of, **insulin receptor kinase** phosphorylation of)
RN 141349-62-4 HCAPLUS
CN Phosphoprotein IRS 1 (rat clone C18/S27 protein moiety reduced) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **88201-45-0**, **Insulin receptor kinase**
RL: BIOL (Biological study)
(**insulin receptor** substrate-1 recognition by, YMXM motif in)
RN 88201-45-0 HCAPLUS
CN Kinase (phosphorylating), insulin receptor (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **143376-54-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with **insulin receptor kinase**, kinetics of, enzyme recognition motifs in relation to)
RN 143376-54-9 HCAPLUS
CN L-Aspartic acid, L-lysyl-L-lysyl-L-lysyl-L-leucyl-L-prolyl-L-alanyl-L-threonylglycyl-L-α-aspartyl-L-tyrosyl-L-methionyl-L-asparaginyl-L-methionyl-L-seryl-L-prolyl-L-valylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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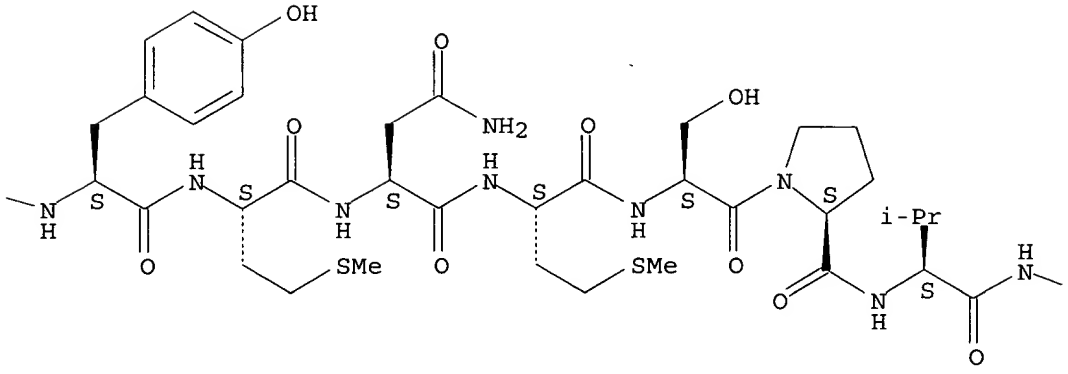

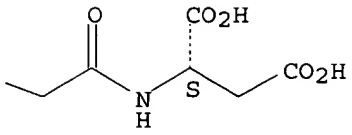

L26 ANSWER 14 OF 14 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1992:228381 HCAPLUS
DOCUMENT NUMBER: 116:228381
TITLE: Structure of the insulin receptor substrate IRS-1 defines a unique signal transduction protein
AUTHOR(S): Sun, Xiao Jian; Rothenberg, Paul; Kahn, C. Ronald; Backer, Jonathan M.; Araki, Eiichi; Wilden, Peter A.; Cahill, Deborah A.; Goldstein, Barry J.; White, Morris F.
CORPORATE SOURCE: Dep. Med., Harvard Med. Sch., Boston, MA, 02215, USA
SOURCE: Nature (London, United Kingdom) (1991), 352(6330), 73-7
CODEN: NATUAS; ISSN: 0028-0836
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **insulin receptor** substrate IRS-1, which encodes a component of the pp185 band was cloned. IRS-1 contains over ten potential tyrosine phosphorylation sites, six of which are in Tyr-Met-X-Met motifs. During **insulin** stimulation, the IRS-1 protein undergoes tyrosine phosphorylation and binds phosphatidylinositol 3-**kinase**, suggesting that IRS-1 acts as a multisite docking protein to bind signal-transducing mols. containing Src-homol. 2 and Src-homol.-3 domains. Thus IRS-1 may link the **insulin receptor** **kinase** and enzymes regulating cellular growth and metabolism
IT **141349-62-4**, Phosphoprotein IRS 1 (rat clone C18/S27 protein moiety reduced)
RL: PRP (Properties)
(amino acid sequence of, complete)
RN 141349-62-4 HCAPLUS
CN Phosphoprotein IRS 1 (rat clone C18/S27 protein moiety reduced) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

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L1           161 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("COLE PHIL"/AU OR "COLE
                 PHILIP"/AU OR "COLE PHILIP A"/AU OR "COLE PHILIP ARTHUR"/AU)
                 OR  COLE P/AU OR  COLE P A/AU
L2            57 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("PARANG K"/AU OR "PARANG
                 KAYKAVOOS"/AU OR "PARANG KEYKAVOUS"/AU)
L3             8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("ABLOOGLU ARARAT J"/AU OR
                 "ABLOOGLU ARARAT JAN"/AU OR "ABLOOGU ARARAT"/AU) NOT L2
L4            45 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("KOHANSKI R"/AU OR "KOHANSKI
                 R A"/AU OR "KOHANSKI RON"/AU OR "KOHANSKI RON A"/AU OR
                 "KOHANSKI RONALD"/AU OR "KOHANSKI RONALD A"/AU) NOT (L2 OR L3)
L5            22 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ("COURTNEY A"/AU OR "COURTNEY
                 A D"/AU OR ("COURTNEY ALIYA"/AU OR "COURTNEY ALIYA D"/AU)) NOT
                 (L2 OR L3 OR L4)
L6           151 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 NOT (L2 OR L3 OR L4 OR L5)

L7            64 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L6 AND (BISUB? OR INHIBITOR
                 OR KINASE)
L15              STR
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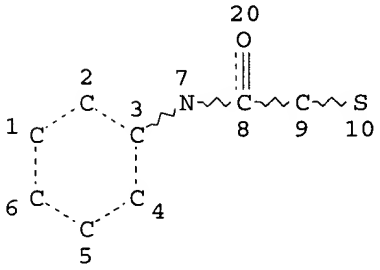


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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  11

STEREO ATTRIBUTES: NONE
L17       125972 SEA FILE=REGISTRY SSS FUL L15
L18              STR
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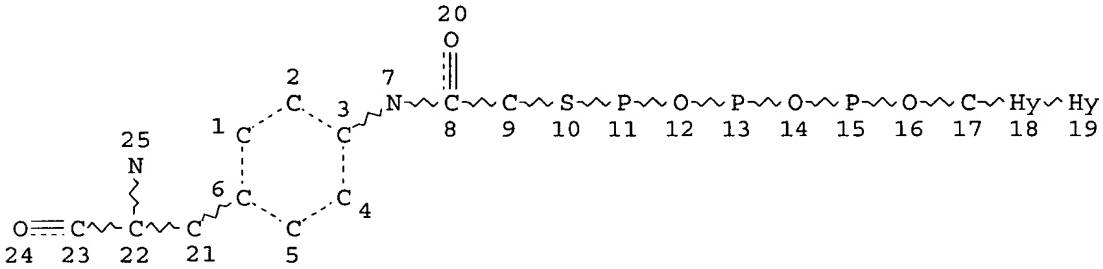


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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
GGCAT   IS MCY  AT  18
GGCAT   IS PCY  AT  19
DEFAULT ECLEVEL IS LIMITED
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GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  25

STEREO ATTRIBUTES: NONE
L19           6 SEA FILE=REGISTRY SUB=L17 SSS FUL L18
L20          45 SEA FILE=REGISTRY ABB=ON  PLU=ON  KKKLPATGD|MNMSPVGD/SQSP
L21           4 SEA FILE=REGISTRY ABB=ON  PLU=ON  ("INSULIN RECEPTOR KINASE"/CN
                 OR "INSULIN RECEPTOR KINASE (SYCON RAPHANUS ISOFORM 1)"/CN OR
                "INSULIN RECEPTOR KINASE (SYCON RAPHANUS ISOFORM 2)"/CN OR
                "INSULIN RECEPTOR KINASE (SYCON RAPHANUS ISOFORM 3)"/CN)
L22           4 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L19
L23          41 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L20
L24        6708 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L21 OR INSULIN(L)RECEPTOR(L)KI
                NASE
L25          17 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L24 AND L23
L26          14 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L25 NOT L22
L27          24 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L23 NOT (L2 OR L3 OR L4 OR L5
                OR L7 OR L22 OR L26)


=> d ibib abs hitstr l27 1-24

L27  ANSWER 1 OF 24  HCAPLUS  COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER:         2005:588338  HCAPLUS
DOCUMENT NUMBER:          143:72805
TITLE:                    Polymorphisms in known genes associated with type II
                          diabetes and obesity and methods of detection and uses
INVENTOR(S):              Venter, J. Craig; Zhang, Jinghui N.; Liu, Xiangjun;
                          Rowe, William; Cravchik, Anibal; Kalush, Francis;
                          Naik, Ashwinikumar; Subramanian, Gangadharan; Woodage,
                          Trevor
PATENT ASSIGNEE(S):       Applera Corp., USA
SOURCE:                   U.S. Pat. Appl. Publ., 31 pp., Cont. of U.S. Ser. No.
                          948,947, abandoned.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.          DATE
     ---------------      ----   --------    --------------------     --------
     US 2005147987         A1    20050707    US 2004-893315           20040719
PRIORITY APPLN. INFO.:                       US 2000-231397P      P   20000908
                                             US 2001-948947       B1  20010910
AB   The present invention is based on the discovery of 1988 novel
     polymorphisms (SNPs) in 61 genes known in the art to contribute to type II
     diabetes and obesity.  Such polymorphisms can lead to a variety of
     disorders that are mediated/modulated by a variant type II diabetes and
     obesity associated protein.  The present invention provides reagents used for
     detecting and expressing the variant nucleic acid/protein sequence as well
     as methods of identifying and using these variants.
IT   855029-97-9
     RL: ADV (Adverse effect, including toxicity); ANT (Analyte); DGN
     (Diagnostic use); PRP (Properties); ANST (Analytical study); BIOL
     (Biological study); USES (Uses)
        (amino acid sequence; polymorphisms in known genes associated with type II
        diabetes and obesity and methods of detection and uses)
```

RN 855029-97-9 HCAPLUS
CN Type II diabetes and obesity-associated protein (human clone US20050147987-SEQID-97)) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 2 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:547044 HCAPLUS
DOCUMENT NUMBER: 143:76253
TITLE: cDNA microarray technology identifies obesity-related gene expression profiles in fat tissue, which may be useful for development of obesity treatments in humans
INVENTOR(S): Clerc, Roger G.; Duchateau-Nguyen, Guillemette; Gardes, Christophe; Mizrahi, Jacques; Ostenson, Claes-Goran
PATENT ASSIGNEE(S): Switz.
SOURCE: U.S. Pat. Appl. Publ., 21 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005136465	A1	20050623	US 2004-19829	20041222
EP 1548445	A2	20050629	EP 2004-29641	20041215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU				
CA 2487098	AA	20050622	CA 2004-2487098	20041221
JP 2005176846	A2	20050707	JP 2004-370470	20041222
PRIORITY APPLN. INFO.:			EP 2003-104902 A	20031222

AB The present invention relates to novel targets for identifying compds. that may be useful for the prevention and treatment of obesity. CDNA microarray anal., using RNA extracted from human fat tissue, was performed to identify obesity-related changes in gene expression profiles. A total of 146 candidate gene or protein sequences were identified. The goal of this work is to develop preventions or treatments for obesity in humans.
IT **855025-84-2**
RL: BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amino acid sequence; cDNA microarray technol. identifies obesity-related gene expression profiles in fat tissue, which may be useful for development of obesity treatments in humans)
RN 855025-84-2 HCAPLUS
CN Protein IRS-1 (insulin receptor substrate 1) (human 1242-amino acid) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 3 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:497224 HCAPLUS
DOCUMENT NUMBER: 143:38377
TITLE: Sequences of a human aspartyl (asparaginyl) β-hydroxylase (HAAH) and use for diagnosis and treatment of pancreatic cancer
INVENTOR(S): Wands, Jack R.; De La Monte, Suzanne M.; Deutch, Alan H.; Ghanbari, Hossein A.
PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 52 pp., Cont.-in-part of U.S. Ser. No. 436,184.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005123545	A1	20050609	US 2004-918685		20040813
US 2003031670	A1	20030213	US 1999-436184		19991108
PRIORITY APPLN. INFO.:			US 1999-436184	A2	19991108
			US 2003-494896P	P	20030813

AB The invention features a method of inhibiting tumor growth and/or tumor invasiveness in a mammal by administering to a mammal a compound (e.g., an antagonistic antibody) which inhibits expression or enzymic activity of human aspartyl (asparaginyl) β-hydroxylase (HAAH). The invention also features a method for diagnosing the growth of a malignant neoplasm (e.g., pancreatic cancer) in a mammal by contacting a tissue or bodily fluid from the mammal with an antibody which binds to a HAAH polypeptide under conditions sufficient to form an antigen-antibody complex and/or detecting the antigen-antibody complex.

IT **853285-80-0**
RL: PRP (Properties)
(unclaimed protein sequence; sequences of a human aspartyl (asparaginyl) β-hydroxylase (HAAH) and use for diagnosis and treatment of pancreatic cancer)
RN 853285-80-0 HCAPLUS
CN 5: PN: US20050123545 SEQID: 5 unclaimed protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 4 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2005:158511 HCAPLUS
DOCUMENT NUMBER: 142:259951
TITLE: Diagnosis and treatment of pancreatic carcinoma by detecting and inhibiting aspartylpeptide β-di-oxygenase
INVENTOR(S): Wands, Jack R.; De La Monte, Suzanne M.; Deutch, Alan H.; Ghanbari, Hossein A.
PATENT ASSIGNEE(S): Rhode Island Hospital, USA
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005016281	A2	20050224	WO 2004-US26336	20040813

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,

EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-494896P P 20030813

AB The invention features a method of inhibiting tumor growth and/or tumor invasiveness in a mammal by administering to a mammal a compound (e.g., an antagonistic antibody) which inhibits expression or enzymic activity of human aspartylpeptide β-di-oxygenase. The invention also features a method for diagnosing the growth of a malignant neoplasm (e.g., pancreatic cancer) in a mammal by contacting a tissue or bodily fluid from the mammal with an antibody which binds to a HAAH polypeptide under conditions sufficient to form an antigen-antibody complex and/or detecting the antigen-antibody complex.

IT **845703-57-3**
RL: PRP (Properties)
(unclaimed protein sequence; diagnosis and treatment of pancreatic carcinoma by detecting and inhibiting aspartylpeptide β-di-oxygenase)

RN 845703-57-3 HCAPLUS

CN 6: PN: WO2005016281 SEQID: 5 unclaimed protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 5 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2005:9198 HCAPLUS

DOCUMENT NUMBER: 142:91478

TITLE: Gene expression profiles in rheumatoid arthritis and osteoarthritis and their use in diagnosis and monitoring disease progress

INVENTOR(S): Blaess, Stefan

PATENT ASSIGNEE(S): Germany

SOURCE: Ger. Offen., 89 pp.
CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10328033	A1	20050105	DE 2003-10328033	20030619

PRIORITY APPLN. INFO.: DE 2003-10328033 20030619

AB DNA microarrays that can be used to diagnose and monitor rheumatoid arthritis (RA) and osteoarthritis (OA) are described. Gene expression is analyzed using software that can compare m-dimensional gene expression profiles multi-parametrical with n-dimensional reference gene expression profiles for diagnostics, sub diagnostics classification and therapy decisions.

IT **481200-98-0**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; gene expression profiles in rheumatoid arthritis and osteoarthritis and their use in diagnosis and monitoring disease progress)

RN 481200-98-0 HCAPLUS

CN Insulin receptor substrate-1 (human gene insulin receptor substrate-1, IRS-1) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 6 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:979655 HCAPLUS
DOCUMENT NUMBER: 142:18205
TITLE: The status, quality, and expansion of the NIH full-length cDNA project: The mammalian gene collection (MGC)
AUTHOR(S): Gerhard, Daniela S.; Wagner, Lukas; Feingold, Elise A.; Shenmen, Carolyn M.; Grouse, Lynette H.; Schuler, Greg; Klein, Steven L.; Old, Susan; Rasooly, Rebekah; Good, Peter; Guyer, Mark; Peck, Allicon M.; Derge, Jeffery G.; Lipman, David; Collins, Francis S.
CORPORATE SOURCE: The MGC Project Team, NIH, USA
SOURCE: Genome Research (2004), 14(10b), 2121-2127
CODEN: GEREFS; ISSN: 1088-9051
PUBLISHER: Cold Spring Harbor Laboratory Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The National Institutes of Health's Mammalian Gene Collection (MGC) project was designed to generate and sequence a publicly accessible cDNA resource containing a complete open reading frame (ORF) for every human and mouse gene. The project initially used a random strategy to select clones from a large number of cDNA libraries from diverse tissues. Candidate clones were chosen based on 5'-EST sequences, and then fully sequenced to high accuracy and analyzed by algorithms developed for this project. Currently, more than 11,000 human and 10,000 mouse genes are represented in MGC by at least one clone with a full ORF. The random selection approach is now reaching a saturation point, and a transition to protocols targeted at the missing transcripts is now required to complete the mouse and human collections. Comparison of the sequence of the MGC clones to reference genome sequences reveals that most cDNA clones are of very high sequence quality, although it is likely that some cDNAs may carry missense variants as a consequence of exptl. artifact, such as PCR, cloning, or reverse transcriptase errors. Recently, a rat cDNA component was added to the project, and ongoing frog (Xenopus) and zebrafish (Danio) cDNA projects were expanded to take advantage of the high-throughput MGC pipeline. The sequence data for the full-length clones from this study have been submitted to GenBank/EMBL/DDBJ under accession nos. BC000001-BC077073. [This abstr record is one of 39 records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].
IT **625303-37-9**, GenBank AAH53895
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; status, quality, and expansion of the NIH full-length cDNA project and mammalian gene collection (MGC))
RN 625303-37-9 HCAPLUS
CN Insulin receptor substrate 1 (human clone MGC:61462 IMAGE:6144252) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 7 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:449883 HCAPLUS
DOCUMENT NUMBER: 140:402911
TITLE: Binary prediction tree modeling with many predictors and its uses in clinical and genomic applications
INVENTOR(S): Nevins, Joseph R.; West, Mike; Huang, Andrew T.
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 886 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004038376	A2	20040506	WO 2003-XA33946	20031024
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2004038376	A2	20040506	WO 2003-US33946	20031024
WO 2004038376	A3	20040826		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:		
US 2002-420729P	P	20021024
US 2002-421062P	P	20021025
US 2002-421102P	P	20021025
US 2002-424701P	P	20021108
US 2002-424715P	P	20021108
US 2002-424718P	P	20021108
US 2002-425256P	P	20021112
US 2003-448461P	P	20030221
US 2003-448462P	P	20030221
US 2003-457877P	P	20030327
US 2003-458373P	P	20030331
WO 2003-US33946	A	20031024

AB The statistical anal. described and claimed is a predictive statistical tree model that overcomes several problems observed in prior statistical models and regression analyses, while ensuring greater accuracy and predictive capabilities. Although the claimed use of the predictive statistical tree model described herein is directed to the prediction of a disease in individuals, the claimed model can be used for a variety of applications including the prediction of disease states, susceptibility of disease states or any other biol. state of interest, as well as other applicable non-biol. states of interest. This model first screens genes to reduce noise, applies kmeans correlation-based clustering targeting a large number of clusters, and then uses singular value decompns. (SVD) to extract the single dominant factor (principal component) from each cluster. This generates a statistically significant number of cluster-derived singular factors, that are referred to as metagenes, that characterize multiple patterns of expression of the genes across samples. The strategy aims to extract multiple such patterns while reducing dimension and smoothing out gene-specific noise through the aggregation within clusters. Formal

predictive anal. then uses these metagenes in a Bayesian classification tree anal. This generates multiple recursive partitions of the sample into subgroups (the 'leaves' of the classification tree), and assocs. Bayesian predictive probabilities of outcomes with each subgroup. Overall predictions for an individual sample are then generated by averaging predictions, with appropriate wts., across many such tree models. The model includes the use of iterative out-of-sample, cross-validation predictions leaving each sample out of the data set one at a time, refitting the model from the remaining samples and using it to predict the hold-out case. This rigorously tests the predictive value of a model and mirrors the real-world prognostic context where prediction of new cases as they arise is the major goal.

IT **481200-98-0**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; binary prediction tree modeling with many predictors and its uses in clin. and genomic applications)

RN 481200-98-0 HCAPLUS

CN Insulin receptor substrate-1 (human gene insulin receptor substrate-1, IRS-1) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 8 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:219931 HCAPLUS
DOCUMENT NUMBER: 140:248186
TITLE: Use of patterns of gene expression to identify tissue types and in disease diagnosis and prognosis
INVENTOR(S): Glinskii, Guennadi V.
PATENT ASSIGNEE(S): Sidney Kimmel Cancer Center, USA
SOURCE: U.S. Pat. Appl. Publ., 209 pp., which which which which
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004053317	A1	20040318	US 2003-660434		20030910
CA 2498418	AA	20040325	CA 2003-2498418		20030910
WO 2004025258	A2	20040325	WO 2003-US28707		20030910
WO 2004025258	A3	20050519			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
EP 1552293	A2	20050713	EP 2003-759240		20030910
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
US 2005142573	A1	20050630	US 2004-861003		20040603
PRIORITY APPLN. INFO.:			US 2002-410018P	P	20020910
			US 2002-411155P	P	20020916

US 2002-429168P	P	20021125
US 2003-444348P	P	20030131
US 2003-460826P	P	20030403
US 2003-660434	A1	20030910
WO 2003-US28707	W	20030910

AB Methods of using quant. anal. of array hybridizations to identify normal and diseased tissue in the diagnosis and prognosis of disease are described. The methods segregate individual samples into distinct classes using quant. measurements of expression values for selected sets of genes in individual samples compared to a reference standard Samples displaying pos. and neg. correlations of the gene expression values with the reference standard samples exhibit distinct behaviors and pathohistol. features. Also disclosed are methods for identifying sets of genes whose expression patterns are correlated with a phenotype. Such sets are useful for characterizing cellular differentiation pathways and states and for identifying potential drug discovery targets. Panels for diagnosis and determination of risk of invasive and metastatic forms of lung, prostate and breast cancer are identified. Similarly, panels indicating recurrence of the cancers and poor prognostic outcomes are identified.

IT **481200-98-0**
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); BIOL (Biological study); USES (Uses)
(amino acid sequence; use of patterns of gene expression to identify tissue types and in disease diagnosis and prognosis)

RN 481200-98-0 HCAPLUS

CN Insulin receptor substrate-1 (human gene insulin receptor substrate-1, IRS-1) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 9 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER:	2004:80714 HCAPLUS
DOCUMENT NUMBER:	140:141434
TITLE:	Human protein sequences of protein complexes of cellular networks underlying the development of cancer and other diseases
INVENTOR(S):	Merino, Alejandro; Bouwmeester, Tewis; Bauer, Andreas; Drewes, Gerard; Marzioch, Martina; Kruse, Ulrich; Superti-Furga, Giulio; Eberhard, Dirk; Ruffner, Heinz; Hobson, Scott; Helftenbein, Gerd; Cruciat, Cristina
PATENT ASSIGNEE(S):	Cellzome Ag, Germany; et al.
SOURCE:	PCT Int. Appl., 810 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004009622	A2	20040129	WO 2003-EP7835	20030718
WO 2004009622	A3	20040910		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: EP 2002-16109 A 20020719
EP 2002-16111 A 20020719
EP 2002-16123 A 20020719
EP 2002-16128 A 20020719
EP 2002-16427 A 20020722

AB The present invention relates to protein complexes involved in cellular processes which have been shown to be critical for the development of various forms of cancer, component proteins of the said complexes, fragments and derivs. of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the complexes and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

IT **652210-78-1**, Protein (human)
RL: DGN (Diagnostic use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(amino acid sequence; human protein sequences of protein complexes of cellular networks underlying the development of cancer and other diseases)

RN 652210-78-1 HCAPLUS
CN Protein (human) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 10 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:942767 HCAPLUS
DOCUMENT NUMBER: 140:40262
TITLE: Genes expressed in atherosclerotic tissue and their use in diagnosis and pharmacogenetics
INVENTOR(S): Nevins, Joseph; West, Mike; Goldschmidt, Pascal
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 408 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003091391	A2	20031106	WO 2002-XB38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003091391	A2	20031106	WO 2002-US38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW				

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-374547P P 20020423
US 2002-420784P P 20021024
US 2002-421043P P 20021025
US 2002-424680P P 20021108
WO 2002-US38221 A 20021112

AB Genes whose expression is correlated with an determinant of an atherosclerotic phenotype are provided. Also provided are methods of using the subject atherosclerotic determinant genes in diagnosis and treatment methods, as well as drug screening methods. In addition, reagents and kits thereof that find use in practicing the subject methods are provided. Also provided are methods of determining whether a gene is correlated with a disease phenotype, where correlation is determined using a Bayesian anal. [This abstract record is one of three records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

IT **481200-98-0**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; genes expressed in atherosclerotic tissue and their use in diagnosis and pharmacogenetics)

RN 481200-98-0 HCAPLUS

CN Insulin receptor substrate-1 (human gene insulin receptor substrate-1, IRS-1) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 11 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:942764 HCAPLUS
DOCUMENT NUMBER: 140:3792
TITLE: Genes expressed in atherosclerotic tissue and their use in diagnosis and pharmacogenetics
INVENTOR(S): Nevins, Joseph; West, Mike; Goldschmidt, Pascal
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 408 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003091391	A2	20031106	WO 2002-XA38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
WO 2003091391	A2	20031106	WO 2002-US38221	20021112
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,				

DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
US 2002-374547P P 20020423
US 2002-420784P P 20021024
US 2002-421043P P 20021025
US 2002-424680P P 20021108
WO 2002-US38221 A 20021112

AB Genes whose expression is correlated with an determinant of an atherosclerotic phenotype are provided. Also provided are methods of using the subject atherosclerotic determinant genes in diagnosis and treatment methods, as well as drug screening methods. In addition, reagents and kits thereof that find use in practicing the subject methods are provided. Also provided are methods of determining whether a gene is correlated with a disease phenotype, where correlation is determined using a Bayesian anal.

IT **481200-98-0**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; genes expressed in atherosclerotic tissue and their use in diagnosis and pharmacogenetics)

RN 481200-98-0 HCAPLUS
CN Insulin receptor substrate-1 (human gene insulin receptor substrate-1, IRS-1) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 12 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:913280 HCAPLUS
DOCUMENT NUMBER: 139:379453
TITLE: Genes showing altered patterns of expression in multiple sclerosis and their diagnostic and therapeutic uses
INVENTOR(S): Dangond, Fernando; Hwang, Daehee
PATENT ASSIGNEE(S): Brigham and Women's Hospital, Inc., USA
SOURCE: PCT Int. Appl., 148 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003095618	A2	20031120	WO 2003-US14462	20030507
WO 2003095618	A3	20041021		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,

FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004018522 A1 20040129 US 2003-430762 20030506
PRIORITY APPLN. INFO.: US 2002-379284P P 20020509
US 2003-430762 A1 20030506

AB The present invention identifies a number of gene markers whose expression is altered in multiple sclerosis (MS). These markers can be used to diagnose or predict MS in subjects, and can be used in the monitoring of therapies. In addition, these genes identify therapeutic targets, the modification of which may prevent MS development or progression. Genes were identified by determination of expression profiling. A large number of genes showing altered patterns of expression were identified, with the most discriminatory genes being those for: phosphatidylinositol transfer protein, inducible nitric oxide synthase, CIC-1 (CLCN1) muscle chloride channel protein, placental bikunin (AMBP), receptor kinase ligand LERK-3/Ephrin-A3, GATA-4, thymopoietin, transcription factor E2f-2, S-adenosylmethionine synthetase, carcinoembryonic antigen, the ret oncogene, a G protein-linked receptor (clone GPCR W), GTP- binding protein RALB, tyrosine kinase Syk, LERK-2/Ephrin-B1, ELK1 tyrosine kinase oncogene, transcription factor SL1, phospholipase C, gastricsin (progastricsin), and the D13S824E locus.

IT **481200-98-0**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; genes showing altered patterns of expression in multiple sclerosis and their diagnostic and therapeutic uses)

RN 481200-98-0 HCAPLUS
CN Insulin receptor substrate-1 (human gene insulin receptor substrate-1, IRS-1) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 13 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:551621 HCAPLUS
DOCUMENT NUMBER: 139:129924
TITLE: CRISSP method for detecting remote sequence homologs, human protein kinase sequences identified with the method, and diagnostic and drug screening uses
INVENTOR(S): Grigoriev, Igor Vyacheslavovich; Sudarsanam, Sucha
PATENT ASSIGNEE(S): Sugen Inc., USA
SOURCE: PCT Int. Appl., 491 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003057841	A2	20030717	WO 2002-US41687	20021231
WO 2003057841	C1	20040401		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004009549 A1 20040115 US 2002-334143 20021231
EP 1576087 A2 20050921 EP 2002-799335 20021231
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK
WO 2004069154 A2 20040819 WO 2003-US2234 20030128
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2001-343169P P 20011231
WO 2002-US41687 W 20021231

AB The present invention relates to novel methods for detecting remote polypeptide homologs comprising anal. of conserved secondary structure pattern in a protein family, and conserved active site amino acid residues. The anal. are used to identify conserved residues embedded into the secondary structure pattern (CRISSP), which are used to detect remote homologs of the referent protein family. The present invention also relates to human protein kinases and protein kinase-like enzymes, nucleotide sequences encoding the protein kinase polypeptides, as well as various products and methods useful for the diagnosis and treatment of various protein kinase-related diseases and conditions. The CRISSP method has been applied to the human genome database and 87 novel kinase sequences have been identified. The partial or complete sequences of these kinases are provided together with their classification, predicted protein structure, and encoding nucleotide sequences. Through the use of a bioinformatics strategy, mammalian protein kinases have been identified and their protein structure predicted.

IT **564491-02-7DP**, subfragments are claimed
RL: ANT (Analyte); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BUU (Biological use, unclassified); DGN (Diagnostic use); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; CRISSP method for detecting remote sequence homologs, human protein kinase sequences identified with the method, and diagnostic and drug screening uses)

RN 564491-02-7 HCAPLUS

CN Protein (human gene 36909 protein kinase sequence homolog fragment) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 14 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:7680 HCAPLUS
DOCUMENT NUMBER: 138:164521
TITLE: Analysis of the mouse transcriptome based on functional annotation of 60,770 full-length cDNAs
AUTHOR(S): Okazaki, Y.; Furuno, M.; Kasukawa, T.; Adachi, J.; Bono, H.; Kondo, S.; Nikaido, I.; Osato, N.; Saito, R.; Suzuki, H.; Yamanaka, I.; Kiyosawa, H.; Yagi, K.; Tomaru, Y.; Hasegawa, Y.; Nogami, A.; Schoenbach, C.; Gojobori, T.; Baldarelli, R.; Hill, D. P.; Bult, C.; Hume, D. A.; Quackenbush, J.; Schriml, L. M.; Kanapin, A.; Matsuda, H.; Batalov, S.; Beisel, K. W.; Blake, J. A.; Bradt, D.; Brusic, V.; Chothia, C.; Corbani, L.

E.; Cousins, S.; Dalla, E.; Dragani, T. A.; Fletcher, C. F.; Forrest, A.; Frazer, K. S.; Gaasterland, T.; Gariboldi, M.; Gissi, C.; Godzik, A.; Gough, J.; Grimmond, S.; Gustincich, S.; Hirokawa, N.; Jackson, I. J.; Jarvis, E. D.; Kanai, A.; Kawaji, H.; Kawasawa, Y.; Kedzierski, R. M.; King, B. L.; Konagaya, A.; Kurochkin, I. V.; Lee, Y.; Lenhard, B.; Lyons, P. A.; Maglott, D. R.; Maltais, L.; Marchionni, L.; McKenzie, L.; Miki, H.; Nagashima, T.; Numata, K.; Okido, T.; Pavan, W. J.; Pertea, G.; Pesole, G.; Petrovsky, N.; Pillai, R.; Pontius, J. U.; Qi, D.; Ramachandran, S.; Ravasi, T.; Reed, J. C.; Reed, D. J.; Reid, J.; Ring, B. Z.; Ringwald, M.; Sandelin, A.; Schneider, C.; Semple, C. A. M.; Setou, M.; Shimada, K.; Sultana, R.; Takenaka, Y.; Taylor, M. S.; Teasdale, R. D.; Tomita, M.; Verardo, R.; Wagner, L.; Wahlestedt, C.; Wang, Y.; Watanabe, Y.; Wells, C.; Wilming, L. G.; Wynshaw-Boris, A.; Yanagisawa, M.; Yang, I.; Yang, L.; Yuan, Z.; Zavolan, M.; Zhu, Y.; Zimmer, A.; Carninci, P.; Hayatsu, N.; Hirozane-Kishikawa, T.; Konno, H.; Nakamura, M.; Sakazume, N.; Sato, K.; Shiraki, T.; Waki, K.; Kawai, J.; Aizawa, K.; Arakawa, T.; Fukuda, S.; Hara, A.; Hashizume, W.; Imotani, K.; Ishii, Y.; Itoh, M.; Kagawa, I.; Miyazaki, A.; Sakai, K.; Sasaki, D.; Shibata, K.; Shinagawa, A.; Yasunishi, A.; Yoshino, M.; Waterston, R.; Lander, E. S.; Rogers, J.; Birney, E.; Hayashizaki, Y.

CORPORATE SOURCE: Laboratory for Genome Exploration Research Group, RIKEN Genomic Sciences Center (GSC), Yokohama Institute, 1-7-22 Suehiro-cho, Tsurumi-ku, Yokohama, Kanagawa, 230-0045, Japan

SOURCE: Nature (London, United Kingdom) (2002), 420(6915), 563-573
CODEN: NATUAS; ISSN: 0028-0836

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Only a small proportion of the mouse genome is transcribed into mature mRNA transcripts. There is an international collaborative effort to identify all full-length mRNA transcripts from the mouse, and to ensure that each is represented in a phys. collection of clones. The manual annotation of 60,770 full-length mouse cDNA sequences is now reported. These are clustered into 33,409 'transcriptional units', contributing 90.1% of a newly established mouse transcriptome database. Of these transcriptional units, 4258 are new protein-coding and 11,665 are new non-coding messages, indicating that non-coding RNA is a major component of the transcriptome. Forty-one percent of all transcriptional units showed evidence of alternative splicing. In protein-coding transcripts, 79% of splice variations altered the protein product. Whole-transcriptome analyses resulted in the identification of 2431 sense-antisense pairs. The present work, completely supported by phys. clones, provides the most comprehensive survey of a mammalian transcriptome so far, and is a valuable resource for functional genomics. The cDNA sequences are deposited in GenBank/EMBL/DDBJ under accession nos. AK002213-AK021412, AK027261-AK054560, AK075567-AK090394, and AK117103-AK117104. [This abstract record is one of thirty records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

IT **493580-91-9**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL

(Biological study)
(amino acid sequence; anal. of the mouse transcriptome based on functional annotation of 60,770 full-length cDNAs)
RN 493580-91-9 HCAPLUS
CN Protein (mouse strain C57BL/6J clone B130064P13 1231-amino acid) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 15 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:977994 HCAPLUS
DOCUMENT NUMBER: 138:49932
TITLE: Antisense oligonucleotides for diagnosis and treatment of angiogenesis-related disorders by inhibition of genes encoding IRS-1 proteins
INVENTOR(S): Al-Mahmood, Salman
PATENT ASSIGNEE(S): Gene Signal, Iraq
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002103014	A2	20021227	WO 2002-FR2067		20020614
WO 2002103014	A3	20040226			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
FR 2826010	A1	20021220	FR 2001-7805		20010614
FR 2826010	B1	20050225			
CA 2451874	AA	20021227	CA 2002-2451874		20020614
EP 1409672	A2	20040421	EP 2002-751246		20020614
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004538272	T2	20041224	JP 2003-505336		20020614
US 2004162257	A1	20040819	US 2003-735512		20031212
PRIORITY APPLN. INFO.:			FR 2001-7805	A	20010614
			WO 2002-FR2067	W	20020614

AB The invention relates to pharmaceutical compns. which inhibit the formation of capillary tubes by endothelial cells, comprising at least one oligonucleotide which can inhibit the expression of the IRS-1 (insulin receptor substrate 1) protein. According to the invention, the oligonucleotides are embodied as anti-angiogenesis agents. Said pharmaceutical compns. are particularly useful in treating angiogenesis-related pathologies.
IT **479165-81-6**
RL: PRP (Properties)
(unclaimed protein sequence; antisense oligonucleotides for diagnosis and treatment of angiogenesis-related disorders by inhibition of genes encoding IRS-1 proteins)

RN 479165-81-6 HCAPLUS
CN 29: PN: WO02103014 SEQID: 29 unclaimed protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 16 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:814183 HCAPLUS
DOCUMENT NUMBER: 137:334056
TITLE: cDNA and protein sequence of human protein IRSAL and the their uses in screening of drugs for treatment of diabetes
INVENTOR(S): Takahashi, Shin-Ichiro; Hakuno, Fumihiko; Kurihara, Shigekazu
PATENT ASSIGNEE(S): Taisho Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002083730	A1	20021024	WO 2002-JP3579	20020410

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 2001-111864 A 20010410
AB This invention provides cDNA and protein sequence of human insulin receptor substrate associated LIM domain containing protein, IRSAL. The IRSAL protein exhibits activity of modifying the physiol. activity of insulin and regulating the intake of carbohydrate into cells. Specifically, the IRSAL regulates the insulin mediated signal transduction by regulation of the tyrosine phosphorylation of insulin receptor and insulin receptor substrate. The IRSAL can be used in screening of drugs for treatment of diabetes.
IT **473863-40-0**
RL: PRP (Properties)
(unclaimed protein sequence; cDNA and protein sequence of human protein IRSAL and the their uses in screening of drugs for treatment of diabetes)
RN 473863-40-0 HCAPLUS
CN 1: PN: WO02083730 SEQID: 1 unclaimed protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 17 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:616205 HCAPLUS
DOCUMENT NUMBER: 137:184452
TITLE: Diagnosis and treatment of malignant neoplasms
INVENTOR(S): Wands, Jack R.; De La Monte, Suzanne M.; Deutch, Alan

H.; Ghanbari, Hossein A.
PATENT ASSIGNEE(S): Rhode Island Hospital, USA
SOURCE: U.S. Pat. Appl. Publ., 34 pp., Cont.-in-part of U. S. Ser. No. 436,184.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002110559	A1	20020815	US 2001-859604	20010517
US 6835370	B2	20041228		
US 2003031670	A1	20030213	US 1999-436184	19991108
US 2002102263	A1	20020801	US 2001-903248	20010711
US 6783758	B2	20040831		
US 2002114810	A1	20020822	US 2001-903063	20010711
US 6815415	B2	20041109		
US 2002114811	A1	20020822	US 2001-903216	20010711
US 6812206	B2	20041102		
US 2002122802	A1	20020905	US 2001-903199	20010711
US 6797696	B2	20040928		
US 2002146421	A1	20021010	US 2001-903023	20010711
CA 2447367	AA	20021121	CA 2002-2447367	20020517
WO 2002092782	A2	20021121	WO 2002-US15814	20020517
WO 2002092782	A3	20040422		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1429797	A2	20040623	EP 2002-731861	20020517
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2005501001	T2	20050113	JP 2002-589650	20020517
US 2005113329	A1	20050526	US 2004-20965	20041223

PRIORITY APPLN. INFO.:
US 1999-436184 A2 19991108
US 2001-859604 A 20010517
WO 2002-US15814 W 20020517

AB The authors disclose a method for diagnosing and inhibiting growth of a malignant neoplasm in a mammal by contacting a cell or a bodily fluid of the mammal with an antibody which binds to an human aspartyl (asparaginyl) beta-hydroxylase (HAAH) polypeptide. Methods of immunization to generate an HAAH-specific immune response are also within the invention.

IT **448985-00-0**
RL: PRP (Properties)
(unclaimed protein sequence; diagnosis and treatment of malignant neoplasms)
RN 448985-00-0 HCAPLUS
CN 4: PN: US20020110559 SEQID: 5 unclaimed protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 18 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:360288 HCAPLUS
DOCUMENT NUMBER: 135:2206
TITLE: Diagnosis and treatment of malignant neoplasms by detecting and inhibiting aspartyl (asparaginyl) β-hydroxylase
INVENTOR(S): Wands, Jack R.; De la Monte, Suzanne M.; Ince, Nedim; Carlson, Rolf I.
PATENT ASSIGNEE(S): Rhode Island Hospital, a Lifespan Partner, USA
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001035102	A2	20010517	WO 2000-US30738	20001108
WO 2001035102	A3	20020912		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2003031670	A1	20030213	US 1999-436184	19991108
CA 2390374	AA	20010517	CA 2000-2390374	20001108
EP 1259813	A2	20021127	EP 2000-978436	20001108
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003519365	T2	20030617	JP 2001-536582	20001108
US 2002102263	A1	20020801	US 2001-903248	20010711
US 6783758	B2	20040831		
US 2002114810	A1	20020822	US 2001-903063	20010711
US 6815415	B2	20041109		
US 2002114811	A1	20020822	US 2001-903216	20010711
US 6812206	B2	20041102		
US 2002122802	A1	20020905	US 2001-903199	20010711
US 6797696	B2	20040928		
US 2002146421	A1	20021010	US 2001-903023	20010711

PRIORITY APPLN. INFO.: US 1999-436184 A2 19991108
WO 2000-US30738 W 20001108

AB The invention features a method for diagnosing a malignant neoplasm in a mammal by contacting a bodily fluid from the mammal with an antibody which binds to an human aspartyl (asparaginyl) β-hydroxylase (HAAH) and methods of treating malignant neoplasms by inhibiting HAAH. Methods of inhibiting tumor growth by contacting a tumor cell with an HAAH antisense nucleic acid are also included.

IT **151086-85-0**, Phosphoprotein IRS-1 (human clone λE36 reduced)
RL: PRP (Properties)
(unclaimed protein sequence; diagnosis and treatment of malignant neoplasms by detecting and inhibiting aspartyl (asparaginyl) β-hydroxylase)

RN 151086-85-0 HCAPLUS

CN Phosphoprotein IRS-1 (human clone λE36 reduced) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 19 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1999:303256 HCAPLUS
DOCUMENT NUMBER: 130:322151
TITLE: Proteins having a PI domain that interacts with the amyloid protein precursor, and their use in the treatment and prevention of Alzheimer's and other neurodegenerative diseases
INVENTOR(S): Sabo, Shasta; Buxbaum, Joseph; Greengard, Paul
PATENT ASSIGNEE(S): The Rockefeller University, USA
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9921995	A1	19990506	WO 1998-US22523		19981023
W: AU, CA, JP, MX					
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
AU 9911979	A1	19990517	AU 1999-11979		19981023
PRIORITY APPLN. INFO.:			US 1997-957660	A	19971024
			US 1998-62085	A	19980417
			WO 1998-US22523	W	19981023

AB The invention discloses the first demonstration that a polypeptide containing a phosphotyrosine interaction (PI) domain interacts with the cytoplasmic domain of the Alzheimer amyloid protein precursor (APP) and that this binding regulates production of beta amyloid (Aβ) by a cell. Thus, by intervening in this interaction, APP processing and trafficking, and hence the progression and/or onset of Alzheimer's disease, can be inhibited or prevented. Hence, the invention provides a cell line for screening agents capable of modulating the interaction of APP with a protein having a PI domain, wherein said cell line over-expresses both APP and the protein. The cell line of the invention is preferably derived from Madin-Darby canine kidney (MDCK) cells but can also be derived from other mammalian cells. In an embodiment of the invention, a MDCK-derived cell line that over-expresses APP and rat Fe65, a brain enriched protein of unknown function which binds to the NPTY sequence in the cytoplasmic tail of APP, is provided. The invention further provides sequences of proteins having PI domains and methods for their use in compns. for the treatment and/or prevention of neurodegenerative diseases, such as Alzheimer's disease and dementia.

IT **151086-87-2**, Phosphoprotein IRS-1 (human clone λE5 reduced)
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(amino acid sequence; proteins having a PI domain that interacts with the amyloid protein precursor, and their use in the treatment and prevention of Alzheimer's and other neurodegenerative diseases)

RN 151086-87-2 HCAPLUS
CN Phosphoprotein IRS-1 (human clone λE5 reduced) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L27 ANSWER 20 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:916029 HCAPLUS
DOCUMENT NUMBER: 124:47072
TITLE: Cloning of a cDNA encoding a 190-kDa insulin receptor substrate-1-like protein of simian COS cells
AUTHOR(S): Wang, Lihong; Hayashi, Hideki; Mitani, Yasumasa; Ishii, Kazuo; Ohnishi, Tetsuo; Niwa, Yasuharu; Kido, Hiroshi; Ebina, Yousuke
CORPORATE SOURCE: Dep. Enzym. Genet., Univ. Tokushima, Tokushima, 770, Japan
SOURCE: Biochemical and Biophysical Research Communications (1995), 216(1), 321-8
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Major insulin signals as stimulation of glucose uptake and DNA synthesis and modification of hexose metabolism are mediated by the tyrosine-phosphorylated insulin receptor substrate-1 (IRS-1; pp180) in many species of cells. We cloned cDNA encoding a 190-kDa IRS 1-like protein (pp190) in simian COS cells and which is slightly larger than IRS-1 (pp180) of human, rat, and mouse cells. The deduced amino acid sequence of COS pp190 consisted of 1251 amino acids and was 96.4%, 87.9% and 88.7% identical to human, mouse and rat IRS-1. The COS pp190 bound to SH2 (src-homol. 2) domains of p85, Grb2/Ash, and SH-PTP2, as did IRS-1. In IRS-1-knockout mice, insulin signals are thought to be mediated by IRS-2 (pp190), which is an alternative signaling mol. and is slightly larger than IRS-1. However, the COS pp190 may be a simian homolog of IRS-1, but not of IRS-2. The results of Southern blotting suggested the possibility that Chinese hamster ovary (CHO) cells have not only the IRS-1 gene but also a gene related to the COS pp190.
IT **172076-41-4**
RL: PRP (Properties)
(amino acid sequence; cloning of a cDNA encoding a 190-kDa insulin receptor substrate-1-like protein of simian COS cells)
RN 172076-41-4 HCAPLUS
CN Protein pp 190 (monkey COS cell insulin receptor substrate-1-like 190-kilodalton) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 21 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1995:444221 HCAPLUS
DOCUMENT NUMBER: 122:262954
TITLE: Mutant cDNA encoding insulin receptor substrate 1
INVENTOR(S): Pedersen, Oluf; Bjoerbaek, Christian; Frederiksen, Kathrine Almind
PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9429345	A1	19941222	WO 1994-DK227	19940610
W: AU, CA, CN, CZ, FI, HU, JP, KR, NO, PL, RU, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9469693	A1	19950103	AU 1994-69693	19940610
EP 711309	A1	19960515	EP 1994-918310	19940610
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
CN 1129001	A	19960814	CN 1994-192962	19940610
CN 1070917	B	20010912		
US 5827730	A	19981027	US 1996-557139	19960212
PRIORITY APPLN. INFO.:			DK 1993-683 A	19930610
			DK 1993-915 A	19930809
			WO 1994-DK227 W	19940610

AB A cDNA encoding a mutant of insulin receptor substrate 1 (IRS-1) is isolated from a patient with non-insulin-dependent diabetes mellitus (NIDDM) by single stranded conformation polymorphism (SSCP) technique and direct DNA sequencing. The cDNA exhibits a G-3494 → A mutation that caused substitution of glycine972 → arginine and 2 silent mutations, i.e., A-2995 → G and G-3262 → C. A further clin. studies indicate that in young obese subjects, the glycine972 → arginine mutation is associated with whole-body insulin resistance and dyslipidemia.

IT **162456-16-8**
RL: PRP (Properties)
(amino acid sequence; cloning of cDNA encoding insulin receptor substrate 1 mutant)

RN 162456-16-8 HCAPLUS

CN Phosphoprotein IRS 1 [972-glycine] (human) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 22 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1994:474840 HCAPLUS

DOCUMENT NUMBER: 121:74840

TITLE: Cloning of the mouse insulin receptor substrate-1 (IRS-1) gene and complete sequence of mouse IRS-1

AUTHOR(S): Araki, Eiichi; Burritt L. Haag III; Kahn, C. Ronald

CORPORATE SOURCE: Research Division, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Joslin Diabetes Center, Room 620, One Joslin Place, Boston, MA, 02215, USA

SOURCE: Biochimica et Biophysica Acta, Molecular Cell Research (1994), 1221(3), 353-6
CODEN: BBAMCO; ISSN: 0167-4889

PUBLISHER: Elsevier B.V.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The mouse IRS-1 gene has been cloned and its structure determined Mouse IRS-1 differs from rat by the absence of the potential C-terminal nucleotide binding site. Otherwise, the predicted IRS-1 protein is highly conserved between mouse, rat and humans, especially in the possible phosphorylation sites.
The highly conserved nature of IRS-1 suggests the importance of these domains in the function of IRS-1 or its association with other proteins.

IT **156532-63-7**, Phosphoprotein IRS-1 (mouse clone λMG2 insulin receptor substrate-1)
RL: PRP (Properties)
(amino acid sequence of)

RN 156532-63-7 HCAPLUS

CN Phosphoprotein IRS 1 (mouse clone λMG2 reduced) (9CI) (CA INDEX

NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 23 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:420841 HCAPLUS
DOCUMENT NUMBER: 119:20841
TITLE: The insulin-elicited 160 kDa phosphotyrosine protein in mouse adipocytes is an insulin receptor substrate 1: identification by cloning
AUTHOR(S): Keller, Susanne R.; Aebersold, Ruedi; Garner, Charles W.; Lienhard, Gustav E.
CORPORATE SOURCE: Dep. Biochem., Dartmouth Med. Sch., Hannover, NH, USA
SOURCE: Biochimica et Biophysica Acta, Gene Structure and Expression (1993), 1172(3), 323-6
CODEN: BBGSD5; ISSN: 0167-4781
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Insulin elicits the tyrosine phosphorylation of one or more proteins of 160-185 kDa in many cell types. Peptide sequences, obtained from this protein purified from mouse 3T3-L1 adipocytes (pp160), were used as the basis for cloning its cDNA. pp160 is highly homologous to the insulin receptor substrate 1, previously cloned from rat liver. Thus, this component of the insulin signaling pathway is the same in adipocytes and in liver.
IT **148221-13-0**, Phosphoprotein IRS-1 (mouse 3T3-L1 adipocyte insulin receptor substrate 1 pp160)
RL: BIOL (Biological study)
(amino acid sequence and insulin-induced phosphorylation of)
RN 148221-13-0 HCAPLUS
CN Phosphoprotein IRS 1 (mouse 3T3-L1 cell reduced) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L27 ANSWER 24 OF 24 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 1993:183912 HCAPLUS
DOCUMENT NUMBER: 118:183912
TITLE: Cloning and increased expression of an insulin receptor substrate-1-like gene in human hepatocellular carcinoma
AUTHOR(S): Nishiyama, Masaki; Wands, Jack R.
CORPORATE SOURCE: Cancer Cent., Massachusetts Gen. Hosp., Boston, MA, 02114, USA
SOURCE: Biochemical and Biophysical Research Communications (1992), 183(1), 280-5
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human insulin receptor substrate-1 (hIRS-1) cDNAs were cloned from a λGT11 expression library using a monoclonal antibody (MAb) produced against a human hepatocellular carcinoma (HCC) cell line (FOCUS). The predicted amino acid sequence derived from both a genomic DNA fragment and the cDNAs showed a 90.5% identity to the previously reported rat IRS-1 cDNA. Multiple potential phosphorylation sites, that suggest an intrinsic function of this mol. in response to insulin action, were highly conserved between the two species. A approx. 180-kDa hIRS-1 protein was immunopptd. and found to be phosphorylated on tyrosine residue(s) following insulin stimulation of HuH-7 HCC cells. Northern blot anal. demonstrated a single approx. 5-kb transcript in HCC cell lines and tissues. Higher levels of

hIRS-1 gene transcripts were observed in HCC tumors compared to adjacent non-involved normal liver.

IT **146811-19-0**
RL: PRP (Properties)
(amino acid sequence of, complete)
RN 146811-19-0 HCAPLUS
CN Phosphoprotein IRS 1 (human reduced) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

=> fil reg
FILE 'REGISTRY' ENTERED AT 12:16:34 ON 06 OCT 2005
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DICTIONARY FILE UPDATES: 5 OCT 2005 HIGHEST RN 864628-18-2

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TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

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*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,   *
* effective March 20, 2005.  A new display format, IDERL, is now    *
* available and contains the CA role and document type information. *
*                                                                    *
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Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

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STRUCTURE FILE UPDATES: 5 OCT 2005 HIGHEST RN 864628-18-2
DICTIONARY FILE UPDATES: 5 OCT 2005 HIGHEST RN 864628-18-2

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

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*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information. *
*                                                                    *
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Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/ONLINE/DBSS/registryss.html

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=> d .seq l20 1-45

L20  ANSWER 1 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   863099-27-8  REGISTRY
CN   INDEX NAME NOT YET ASSIGNED
NTE  modified (modifications unspecified)
SQL  18

SEQ      1 KKKLPATGDF MNTSPVGD
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HITS AT:   1-9

REFERENCE   1:  143:243964

L20  ANSWER 2 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   863099-26-7  REGISTRY
CN   INDEX NAME NOT YET ASSIGNED
NTE  modified (modifications unspecified)
SQL  14

SEQ      1 KKKLPATGDF MNMS
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HITS AT:   1-9

REFERENCE   1:  143:243964

L20  ANSWER 3 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   863099-25-6  REGISTRY
CN   INDEX NAME NOT YET ASSIGNED
NTE  modified (modifications unspecified)
SQL  15

SEQ      1 LPATGDFMNM SPVGD
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HITS AT:    8-15

REFERENCE   1:  143:243964

L20  ANSWER 4 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   863099-23-4  REGISTRY
CN   INDEX NAME NOT YET ASSIGNED
NTE  modified (modifications unspecified)
SQL  18

SEQ      1 KKKLPATGDF MNMSPVGD
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HITS AT:    1-9, 11-18

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

REFERENCE   1:  143:243964

L20  ANSWER 5 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   863099-22-3  REGISTRY
CN   INDEX NAME NOT YET ASSIGNED
NTE  modified (modifications unspecified)
SQL  18

SEQ      1 KKKLPATGDF MNMSPVGD
           =========  ========
HITS AT:    1-9, 11-18

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

REFERENCE   1:  143:243964

L20  ANSWER 6 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   863099-21-2  REGISTRY
CN   INDEX NAME NOT YET ASSIGNED
NTE  modified
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 type            ------ location ------         description
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terminal mod.    Lys-1           -         N-acetyl
modification     Tyr-10          -         undetermined modification
-----------------------------------------------------------------------
SQL  18

SEQ      1 KKKLPATGDY MNMSPVGD
           =========  ========
HITS AT:    1-9, 11-18

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

REFERENCE   1:  143:243964

L20  ANSWER 7 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   855029-97-9  REGISTRY
CN   Type II diabetes and obesity-associated protein (human clone
     US20050147987-SEQID-97)) (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   97: PN: US20050147987 SEQID: 97 claimed protein
SQL  1316
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SEQ    801 PCTGDYMNMS PVGDSNTSSP SDCYYGPEDP QHKPVLSYYS LPRSFKHTQR
                  ==== ====
HITS AT:   807-814

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

REFERENCE   1:  143:72805

L20  ANSWER 8 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   855025-84-2  REGISTRY
CN   Protein IRS-1 (insulin receptor substrate 1) (human 1242-amino acid) (9CI)
     (CA INDEX NAME)
OTHER NAMES:
CN   14: PN: US20050136465 SEQID: 14 claimed protein
SQL  1242

SEQ    701 NGVGGHHSHV LPHPKPPVES SGGKLLPCTG DYMNMSPVGD SNTSSPSDCY
                                                ========
HITS AT:   733-740

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

REFERENCE   1:  143:76253

L20  ANSWER 9 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   853285-80-0  REGISTRY
CN   5: PN: US20050123545 SEQID: 5 unclaimed protein (9CI)  (CA INDEX NAME)
SQL  1242

SEQ    701 NGVGGHHSHV LPHPKPPVES SGGKLLPCTG DYMNMSPVGD SNTSSPSDCY
                                                ========
HITS AT:   733-740

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

REFERENCE   1:  143:38377

L20  ANSWER 10 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   848053-30-5  REGISTRY
CN   L-Aspartic acid, L-lysyl-L-lysyl-L-lysyl-L-leucyl-L-prolyl-L-alanyl-L-
     tyrosylglycyl-L-α-aspartyl-L-tyrosyl-L-methionyl-L-asparaginyl-L-
     methionyl-L-seryl-L-prolyl-L-valylglycyl- (9CI)  (CA INDEX NAME)
SQL  18

SEQ      1 KKKLPAYGDY MNMSPVGD
                      ========
HITS AT:   11-18

REFERENCE   1:  142:311998

L20  ANSWER 11 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   845703-57-3  REGISTRY
CN   6: PN: WO2005016281 SEQID: 5 unclaimed protein (9CI)  (CA INDEX NAME)
SQL  1242

SEQ    701 NGVGGHHSHV LPHPKPPVES SGGKLLPCTG DYMNMSPVGD SNTSSPSDCY
                                                ========
HITS AT:   733-740
```

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 142:259951

L20 ANSWER 12 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 845592-97-4 REGISTRY
CN Kinase (phosphorylating), insulin receptor (rat 1235-amino acids) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 3: PN: EP1508806 SEQID: 16 claimed protein
SQL 1235

SEQ 701 HHTHALPHAK PPVESGGGKL LPCTGDYMNM SPVGDSNTSS PSECYYGPED
=== =====
HITS AT: 728-735

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 142:236028

L20 ANSWER 13 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 841346-72-3 REGISTRY
CN DNA (human clone WO2005012875-SEQID-2417 cyclin-dependent kinase modulator-regulated protein cDNA) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 2417: PN: WO2005012875 SEQID: 2417 claimed protein
SQL 1242

SEQ 701 NGVGGHHSHV LPHPKPPVES SGGKLLPCTG DYMNMSPVGD SNTSSPSDCY
========
HITS AT: 733-740

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 142:214836

L20 ANSWER 14 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 800916-53-4 REGISTRY
CN Protein, IRS-1 (insulin receptor substrate 1) (human) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1: PN: WO2004104220 SEQID: 1 claimed sequence
SQL 1242

SEQ 701 NGVGGHHSHV LPHPKPPVES SGGKLLPCTG DYMNMSPVGD SNTSSPSDCY
========
HITS AT: 733-740

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 142:19236

L20 ANSWER 15 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 800916-52-3 REGISTRY
CN 516-777-Protein, IRS-1 (insulin receptor substrate 1) (human) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 9: PN: WO2004104220 FIGURE: 3 claimed sequence
SQL 262

```
SEQ    201 PPVESSGGKL LPCTGDYMNM SPVGDSNTSS PSDCYYGPED PQHKPVLSYY
                           === =====

HITS AT:   218-225

REFERENCE   1:  142:19236

L20  ANSWER 16 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   732162-72-0  REGISTRY
CN   GenBank AAT99886 (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   GenBank AAT99886 (Translated from: GenBank AY690661)
SQL  1229

SEQ    701 LPHPKLPVES SSGKLLSCTG DYMNMSPVGD SNTSSPSDCY YGPEDPQHKP
                                  ========

HITS AT:   723-730

L20  ANSWER 17 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   688069-62-7  REGISTRY
CN   Protein IRS-1 (insulin receptor substrate 1) (mouse) (9CI)  (CA INDEX
     NAME)
OTHER NAMES:
CN   3: PN: WO2004039963 SEQID: 3 claimed protein
SQL  1231

SEQ    701 HHTHALPHAK PPVESGGGKL LPCTGDYMNM SPVGDSNTSS PSECYYGPED
                                       === =====

HITS AT:   728-735

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

REFERENCE   1:  140:405486

L20  ANSWER 18 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   688069-60-5  REGISTRY
CN   Protein IRS-1 (insulin receptor substrate 1) (human) (9CI)  (CA INDEX
     NAME)
OTHER NAMES:
CN   1: PN: WO2004039963 SEQID: 1 claimed protein
SQL  1242

SEQ    701 NGVGGHHSHV LPHPKPPVES SGGKLLPCTG DYMNMSPVGD SNTSSPSDCY
                                              ========

HITS AT:   733-740

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

REFERENCE   1:  140:405486

L20  ANSWER 19 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   652210-78-1  REGISTRY
CN   Protein (human) (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   189: PN: WO2004009622 SEQID: 189 claimed protein
SQL  1242

SEQ    701 NGVGGHHSHV LPHPKPPVES SGGKLLPCTG DYMNMSPVGD SNTSSPSDCY
                                              ========

HITS AT:   733-740
```

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 140:141434

L20 ANSWER 20 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 625303-37-9 REGISTRY
CN Insulin receptor substrate 1 (human clone MGC:61462 IMAGE:6144252) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank AAH53895
CN GenBank AAH53895 (TRANSLATED FROM: GenBank BC053895)
SQL 1242

SEQ 701 NGVGGHHSHV LPHPKPPVES SGGKLLPCTG DYMNMSPVGD SNTSSPSDCY
========
HITS AT: 733-740

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 142:18205

L20 ANSWER 21 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 623998-86-7 REGISTRY
CN GenBank CAD79961 (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank CAD79961 (TRANSLATED FROM: GenBank AX659634)
SQL 1242

SEQ 701 NGVGGHHSHV LPHPKPPVES SGGKLLPCTG DYMNMSPVGD SNTSSPSDCY
========
HITS AT: 733-740

RELATED SEQUENCES AVAILABLE WITH SEQLINK

L20 ANSWER 22 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 564491-02-7 REGISTRY
CN Protein (human gene 36909 protein kinase sequence homolog fragment) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 18: PN: WO03057841 FIGURE: 2 claimed sequence
SQL 1316

SEQ 801 PCTGDYMNMS PVGDSNTSSP SDCYYGPEDP QHKPVLSYYS LPRSFKHTQR
==== ====
HITS AT: 807-814

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 139:129924

L20 ANSWER 23 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 493580-91-9 REGISTRY
CN Protein (mouse strain C57BL/6J clone B130064P13 1231-amino acid) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank BAC32308
CN GenBank BAC32308 (Translated from: GenBank AK045317)
SQL 1231

SEQ 701 HHTHALPHAK PPVESGGGKL LPCTGDYMNM SPVGDSNTSS PSECYYGPED

                                        === =====
HITS AT: 728-735

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 138:164521

L20 ANSWER 24 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 487716-78-9 REGISTRY
CN GenBank CAA41264 (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank CAA41264 (Translated from: GenBank X58375)
SQL 1235

SEQ 701 HHTHALPHAK PPVESGGGKL LPCTGDYMNM SPVGDSNTSS PSECYYGPED
                                        === =====
HITS AT: 728-735

RELATED SEQUENCES AVAILABLE WITH SEQLINK

L20 ANSWER 25 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 487639-52-1 REGISTRY
CN GenBank CAA49378 (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank CAA49378 (Translated from: GenBank X69722)
SQL 1231

SEQ 701 HHTHALPHAK PPVESGGGKL LPCTGDYMNM SPVGDSNTSS PSECYYGPED
                                        === =====
HITS AT: 728-735

RELATED SEQUENCES AVAILABLE WITH SEQLINK

L20 ANSWER 26 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 483161-90-6 REGISTRY
CN GenBank AAA39335 (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank AAA39335 (Translated from: GenBank L24563)
SQL 1233

SEQ 701 HHTHALPHAK PPVESGGGKL LPCTGDYMNM SPVGDSNTSS PSECYYGPED
                                        === =====
HITS AT: 728-735

RELATED SEQUENCES AVAILABLE WITH SEQLINK

L20 ANSWER 27 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 481200-98-0 REGISTRY
CN Insulin receptor substrate-1 (human gene insulin receptor substrate-1,
    IRS-1) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1485: PN: WO03095618 TABLE: 1 claimed protein
CN 263: PN: WO03091391 FIGURE: 20 unclaimed protein
CN 2761: PN: WO03091391 TABLE: 20 unclaimed protein
CN 3099: PN: WO2004038376 TABLE: 5 unclaimed protein
CN 648: PN: WO2004087954 PAGE: 70/116 unclaimed protein
CN GenBank AAB27175
CN GenBank AAB27175 (Translated from: GenBank S62539)
SQL 1242

SEQ 701 NGVGGHHSHV LPHPKPPVES SGGKLLPCTG DYMNMSPVGD SNTSSPSDCY
========

HITS AT: 733-740

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 142:91478

REFERENCE 2: 141:325696

REFERENCE 3: 140:402911

REFERENCE 4: 140:248186

REFERENCE 5: 140:40262

REFERENCE 6: 140:3792

REFERENCE 7: 139:379453

L20 ANSWER 28 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 481198-64-5 REGISTRY
CN GenBank AAB21608 (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank AAB21608 (Translated from: GenBank S85963)
SQL 1243

SEQ 701 TNGVGGHHSH VLPHPKPPVE SSGGKLLPCT GDYMNMSPVG DSNTSSPSDC
======= =

HITS AT: 734-741

RELATED SEQUENCES AVAILABLE WITH SEQLINK

L20 ANSWER 29 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 481185-75-5 REGISTRY
CN GenBank BAA11026 (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank BAA11026 (Translated from: GenBank D64157)
SQL 1251

SEQ 701 VGAHNSQVLL HPKPPVESSG GKLLPCTGDY MNMSPVGDSN TSSPSDCYYG
========

HITS AT: 731-738

L20 ANSWER 30 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 479165-81-6 REGISTRY
CN 29: PN: WO02103014 SEQID: 29 unclaimed protein (9CI) (CA INDEX NAME)
SQL 1242

SEQ 701 NGVGGHHSHV LPHPKPPVES SGGKLLPCTG DYMNMSPVGD SNTSSPSDCY
========

HITS AT: 733-740

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 138:49932

L20 ANSWER 31 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 473863-40-0 REGISTRY
CN 1: PN: WO02083730 SEQID: 1 unclaimed protein (9CI) (CA INDEX NAME)

SQL 1235

SEQ 701 HHTHALPHAK PPVESGGGKL LPCTGDYMNM SPVGDSNTSS PSECYYGPED
=== =====

HITS AT: 728-735

REFERENCE 1: 137:334056

L20 ANSWER 32 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 448985-00-0 REGISTRY
CN 4: PN: US20020110559 SEQID: 5 unclaimed protein (9CI) (CA INDEX NAME)
SQL 1242

SEQ 701 NGVGGHHSHV LPHPKPPVES SGGKLLPCTG DYMNMSPVGD SNTSSPSDCY
========

HITS AT: 733-740

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 137:184452

L20 ANSWER 33 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 329783-46-2 REGISTRY
CN L-Aspartic acid, N2-acetyl-L-lysyl-L-lysyl-L-lysyl-L-leucyl-L-prolyl-L-alanyl-L-threonylglycyl-L-α-aspartyl-4-[(bromoacetyl)amino]-L-phenylalanyl-L-methionyl-L-asparaginyl-L-methionyl-L-seryl-L-prolyl-L-valylglycyl- (9CI) (CA INDEX NAME)
NTE modified (modifications unspecified)
SQL 18

SEQ 1 KKKLPATGDF MNMSPVGD
========= ========

HITS AT: 1-9, 11-18

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 134:218831

L20 ANSWER 34 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 329783-44-0 REGISTRY
CN L-Aspartic acid, N2-acetyl-L-lysyl-L-lysyl-L-lysyl-L-leucyl-L-prolyl-L-alanyl-L-threonylglycyl-L-α-aspartyl-4-[[6-(5'-adenylyloxy)-4,6-dihydroxy-4,6-dioxido-1-oxo-5-oxa-3-thia-4,6-diphosphahex-1-yl]amino]-L-phenylalanyl-L-methionyl-L-asparaginyl-L-methionyl-L-seryl-L-prolyl-L-valylglycyl- (9CI) (CA INDEX NAME)
NTE modified (modifications unspecified)
SQL 18

SEQ 1 KKKLPATGDF MNMSPVGD
========= ========

HITS AT: 1-9, 11-18

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 143:243964

REFERENCE 2: 135:253738

REFERENCE 3: 134:218831

L20 ANSWER 35 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 172076-41-4 REGISTRY
CN Protein pp 190 (monkey COS cell insulin receptor substrate-1-like 190-kilodalton) (9CI) (CA INDEX NAME)
SQL 1251

SEQ 701 VGAHNSQVLL HPKPPVESSG GKLLPCTGDY MNMSPVGDSN TSSPSDCYYG
========
HITS AT: 731-738

REFERENCE 1: 124:47072

L20 ANSWER 36 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 162456-16-8 REGISTRY
CN Phosphoprotein IRS 1 [972-glycine] (human) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Insulin receptor substrate 1 [972Gly] (human)
SQL 1243

SEQ 701 TNGVGGHHSH VLPHPKPPVE SSGGKLLPCT GDYMNMSPVG DSNTSSPSDC
======= =
HITS AT: 734-741

REFERENCE 1: 122:262954

L20 ANSWER 37 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 156532-63-7 REGISTRY
CN Phosphoprotein IRS 1 (mouse clone λMG2 reduced) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Phosphoprotein IRS-1 (mouse clone λMG2 insulin receptor substrate-1)
SQL 1233

SEQ 701 HHTHALPHAK PPVESGGGKL LPCTGDYMNM SPVGDSNTSS PSECYYGPED
=== =====
HITS AT: 728-735

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 121:74840

L20 ANSWER 38 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 151086-87-2 REGISTRY
CN Phosphoprotein IRS-1 (human clone λE5 reduced) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Insulin receptor substrate 1 (human clone λE5)
SQL 1242

SEQ 701 NGVGGHHSHV LPHPKPPVES SGGKLLPCTG DYMNMSPVGD SNTSSPSDCY
========
HITS AT: 733-740

REFERENCE 1: 130:322151

REFERENCE 2: 120:97466

L20 ANSWER 39 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 151086-86-1 REGISTRY

```
CN   Phosphoprotein IRS-1 (human clone γE1 reduced) (9CI)  (CA INDEX
     NAME)
OTHER NAMES:
CN   Insulin receptor substrate 1 (human clone γE1)
SQL  1242

SEQ    701 NGVGGHHSHV LPHPKPPVES SGGKLLPCTG DYMNMSPVGD SNTSSPSDCY
                                                 ========
HITS AT:   733-740

REFERENCE   1:  120:97466

L20  ANSWER 40 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   151086-85-0  REGISTRY
CN   Phosphoprotein IRS-1 (human clone λE36 reduced) (9CI)  (CA INDEX
     NAME)
OTHER NAMES:
CN   8: PN: WO0135102 PAGE: 52 unclaimed protein
CN   Insulin receptor substrate 1 (human clone λE36)
SQL  1242

SEQ    701 NGVGGHHSHV LPHPKPPVES SGGKLLPCTG DYMNMSPVGD SNTSSPSDCY
                                                 ========
HITS AT:   733-740

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

REFERENCE   1:  135:2206

REFERENCE   2:  120:97466

L20  ANSWER 41 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   148221-13-0  REGISTRY
CN   Phosphoprotein IRS 1 (mouse 3T3-L1 cell reduced) (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Phosphoprotein IRS-1 (mouse 3T3-L1 adipocyte insulin receptor substrate 1
     pp160)
SQL  1231

SEQ    701 HHTHALPHAK PPVESGGGKL LPCTGDYMNM SPVGDSNTSS PSECYYGPED
                                       === =====
HITS AT:   728-735

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

REFERENCE   1:  119:20841

L20  ANSWER 42 OF 45  REGISTRY  COPYRIGHT 2005 ACS on STN
RN   146811-19-0  REGISTRY
CN   Phosphoprotein IRS 1 (human reduced) (9CI)  (CA INDEX NAME)
SQL  1243

SEQ    701 TNGVGGHHSH VLPHPKPPVE SSGGKLLPCT GDYMNMSPVG DSNTSSPSDC
                                                 ======= =
HITS AT:   734-741

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

REFERENCE   1:  118:183912
```

L20 ANSWER 43 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 145559-05-3 REGISTRY
CN Phosphoprotein IRS 1 (rat clone C18/P2-2) (9CI) (CA INDEX NAME)
SQL 1155

SEQ 651 GKPWTNGVGG HHTHALPHAK PPVESGGGKL LPCTGDYMNM SPVGDSNTSS
=== =====
HITS AT: 688-695

REFERENCE 1: 119:2479

L20 ANSWER 44 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 143376-54-9 REGISTRY
CN L-Aspartic acid, L-lysyl-L-lysyl-L-lysyl-L-leucyl-L-prolyl-L-alanyl-L-threonylglycyl-L-α-aspartyl-L-tyrosyl-L-methionyl-L-asparaginyl-L-methionyl-L-seryl-L-prolyl-L-valylglycyl- (9CI) (CA INDEX NAME)
SQL 18

SEQ 1 KKKLPATGDY MNMSPVGD
========= ========
HITS AT: 1-9, 11-18

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 134:53060

REFERENCE 2: 127:328319

REFERENCE 3: 124:80394

REFERENCE 4: 119:220273

REFERENCE 5: 117:127074

L20 ANSWER 45 OF 45 REGISTRY COPYRIGHT 2005 ACS on STN
RN 141349-62-4 REGISTRY
CN Phosphoprotein IRS 1 (rat clone C18/S27 protein moiety reduced) (9CI) (CA INDEX NAME)
SQL 1235

SEQ 701 HHTHALPHAK PPVESGGGKL LPCTGDYMNM SPVGDSNTSS PSECYYGPED
=== =====
HITS AT: 728-735

RELATED SEQUENCES AVAILABLE WITH SEQLINK

REFERENCE 1: 117:127074

REFERENCE 2: 116:228381

=>